BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 17 1951

THE EXPERIMENTAL APPROACH TO THE PROBLEM OF DIABETES MELLITUS*

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It was said of Sydney Ringer that "clinical medicine was his profession and scientific research his recreation." As one who is a biochemist with an interest in the relationship of the basic sciences to medicine I am particularly honoured to deliver a lecture in memory of a distinguished clinician whose laboratory researches exerted such a fundamental and fruitful influence upon biological science.

The accidental discovery by Mering and Minkowski in 1889, that experimental removal of the pancreas from a dog induces a condition somewhat resembling human diabetes mellitus, supported the simplest view of the aetiology of the human condition—namely, that it was the result of pancreatic deficiency. The pathological observations of Opie and others, based as they were on the earlier histological findings of Langerhans, provided some evidence to this end, and the discovery of insulin by Banting and Best in 1921 still further strengthened this view. Indeed, the unparalleled importance and efficiency of insulin as a therapeutic agent throws into strange contrast our long-continued ignorance of the aetiology of diabetes and of the detailed mechanism of action of insulin.

During the years since the discovery of insulin the idea that human diabetes is always the result of a primary deficiency in the capacity of the pancreas to secrete sufficient insulin for normal needs has become increasingly untenable. For instance, in a small proportion of cases the insulin requirements of the human diabetic may rise to extraordinary high levels, sometimes up to 4,000 units a day for a short time. Such a degree of resistance to the action of insulin can exist without obvious infectious complications, but is happily seldom long maintained.

Arguments based on the insulin requirement of the depancreatized dog and applied to human diabetes are quantitatively dangerous, but they suggest quite a different order of requirement for insulin of the depancreatized human, and in recent years direct observations on human patients depancreatized for therapeutic reasons suggest that their insulin requirement is unlikely to exceed 60 units a day (cf. Waugh *et al.*, 1946). These observations indicate that, in some instances at least, the existence of human diabetes must be associated with factors exerting an action which is antagonistic to that of insulin. That the amount of insulin needed to control human diabetes may vary significantly with the nature of the diet and with other conditions has been stressed, particularly in this country by Himsworth (1949). These observations further emphasize that insulin deficiency alone may not determine the severity of the condition in human diabetes.

*The 19th Sydney Ringer Memorial Lecture, delivered at University College Hospital Medical School, London, on March 16, 1950.

The Diabetogenic Influence of the Pituitary Gland

The path leading to a partial answer to the question of the nature of some factors antagonistic to insulin was indicated by the fundamentally important observations of the Argentinian investigator B. A. Houssay, who, with his colleagues, found that removal of the pituitary gland, or of its anterior lobe only, substantially alleviated the severity of pancreatic diabetes in a variety of species. A corollary of these findings was the induction of a diabetic condition in normal animals by the administration of anterior pituitary extract, and the first striking demonstration of the diabetogenic action of anterior pituitary extract came from the laboratory of H. M. Evans under conditions which we now see to be highly significant.

Evans and his colleagues (1932), with the aim of producing giant animals, treated puppies daily for many months with a growth-promoting extract of anterior pituitary extract. After six to eight months of treatment some of the animals had become ill and were found to be diabetic. This diabetes was associated with an infectious condition of the skin, and the condition persisted for some time after the cessation of pituitary treatment. About this time (1932) Houssay and his pupils succeeded in inducing a diabetic condition in normal and in partially depancreatized animals by a few days of daily treatment with crude anterior pituitary extract (see Houssay and Biasotti, 1932).

We were able to confirm these findings, so far as the diabetogenic activity of crude pituitary extracts was concerned, in intact dogs and cats treated daily for a few days (Young, 1936, 1937). Subsequently we have used intact animals, first the dog and more recently the cat, as test animals for diabetogenic activity, with satisfactorily consistent results, but Houssay and his

colleagues, and also many workers in the United States, have apparently found inconsistent results with intact animals, and have consequently employed dogs or cats from which up to 87% of the pancreas has been surgically removed at a preliminary operation. This operation induces a condition in which the animal very readily exhibits glycosuria after the administration of anterior pituitary extract, but it is one in which the animal's response may be less specific for what we define as the diabetogenic factor of the anterior pituitary gland—that is, a substance whose administration leads to diabetes in an intact animal. Moreover, some partially depancreatized animals may exhibit glycosuria when given control treatment such as the administration of inert protein material. We have had no difficulty in obtaining consistent results with the intact adult dog or cat as test animal and cannot readily account for the difference between our results and those of our colleagues abroad.

While, in our hands, the dog and the cat easily and quickly become diabetic when given daily injections of ox anterior pituitary extract for a few days, many other species of animal do not respond in this way. In fact, the only species which we find to respond consistently to such pituitary treatment by exhibiting diabetes are the dog, the cat, and the ferret. The strains of rabbit we have used do respond, but not consistently, while those convenient laboratory species the rat, the mouse, and the guinea-pig do not become diabetic when given large doses of an extract which is highly diabetogenic in the adult dog and cat. The intact rat, even in an elderly senile condition, always responds to such pituitary treatment, not with diabetes, but with an increased rate of growth. In the laboratory of Professor C. N. H. Long at Yale University the strain of rats is such that partially depancreatized diabetic animals show an increase in the severity of the diabetes when treated with appropriate pituitary extracts, but the strains of rat available to us differ from those in Yale, since we find that treatment of diabetic animals with diabetogenic pituitary extract induces no consistent increase in the severity of the diabetes.

With the intact cat as test animal we found (Cotes, Reid, and Young, 1949) that purified growth hormone is highly diabetogenic, although we could not rule out the possibility that even the most highly purified preparations of growth hormone available to us were contaminated with traces of a substance or substances essential for or contributing to the diabetogenic activity of the growth hormone. Recently Houssay and Anderson (1949), with the partially depancreatized cat or dog as test animal, have found that hyperglycaemia follows the administration of growth hormone, but in cats from which 75% of the pancreas had been surgically removed they administered as much as 25 mg. of purified growth hormone per kilogram of body weight per day in demonstrating this effect. On the other hand, we found (Cotes *et al.*, 1949) that the intact cat would respond with substantial glycosuria to a dose of growth hormone less than 1 mg./kg./day.

Although the diabetogenic activity of pituitary adrenocorticotropin has been demonstrated in the intact rat (Li, Ingle, and Evans) and in the normal human (Conn) we have so far failed to demonstrate a diabetogenic action of adrenocorticotropin in the intact cat in our laboratory, and Dr. E. Reid has administered up to 50 mg./kg./day to the cat without inducing glycosuria. In the dog from which 83–87% of the pancreas had been surgically removed Houssay and Anderson found that 50 mg./kg./day of purified adrenocorticotropin induced a moderate rise of blood sugar in only one dog out of four treated ones, in an experiment lasting four days.

Although adrenocorticotropin must be regarded as a diabetogenic agent under some conditions we believe that the diabetogenic activity of the ox pituitary extracts we have used to be largely attributable to their growth hormone content, although the possibility that a small dose of adrenocorticotropin is present and exerting a co-operative action cannot be ruled out at this stage.

Growth and Pituitary Diabetogenesis

The observed diabetogenic action of growth hormone in the intact adult dog and cat made particularly interesting the results of long-term treatment of the kitten and puppy with diabetogenic-growth-promoting pituitary extracts. As is shown in Table I, large doses of diabetogenic anterior pituitary extracts induced not diabetes but extra growth in puppies and kittens over a period of three weeks, and even in experiments lasting many months the treated kittens and puppies did not become diabetic. Thus it appeared that if the test animal was able to grow, then growth rather than diabetes would occur. Such a view would account for the fact that the intact rat, whose epiphyses never close and which is able always to respond to the administration of growth hormone by growing almost indefinitely, never, in our experience, exhibits diabetes as the result of treatment with growth-promoting anterior pituitary extract. It was therefore of further interest to know whether diabetes would subsequently develop in the long-treated kittens and puppies at a time when they might be regarded as having reached adulthood. So far as the puppy was concerned we did find that a proportion of the long-treated animals developed diabetes (Young, 1941, 1944 ; cf. Evans *et al.*, 1932 ; Evans, 1933). Nevertheless in experiments with over 50 kittens not one became diabetic even when the treatment was continued until after the animal had reached adulthood In this respect the cat which has grown naturally to adulthood differs from the animal whose growth has been hastened by treatment with growth hormone.

TABLE I.—*Diabetogenic Action of Anterior Pituitary Extract (The Values are those Per Kg. of Initial Body Weight)*

	Adult Dog	Adult Cat	Puppy	Kitten
Extract injected daily (mg. equivalent of growth hormone) ..	1·5	0·6	6·0	3·75
Days before onset of glycosuria	4·7	5·6	—	a
First day:				
Glycosuria (g.)	1·97	1·93	—	—
D/N	1·37	1·23	—	—
Second day:				
Glycosuria (g.)	4·63	2·17	—	—
D/N	2·91	1·74	—	—
Net increase in growth rate (g./day)	10·0 (5 days)	8·9 (6 days)	19·1 (21 days)	16·3 (21 days)

We have studied five of the long-treated puppies which subsequently became diabetic. In some of them striking joint changes developed during the early weeks of the experiments, but these changes exerted no obvious course on the growth of the animals, and no differences were observed between the metabolic response of those animals which showed such changes and those which did not. In the long-treated puppies which became

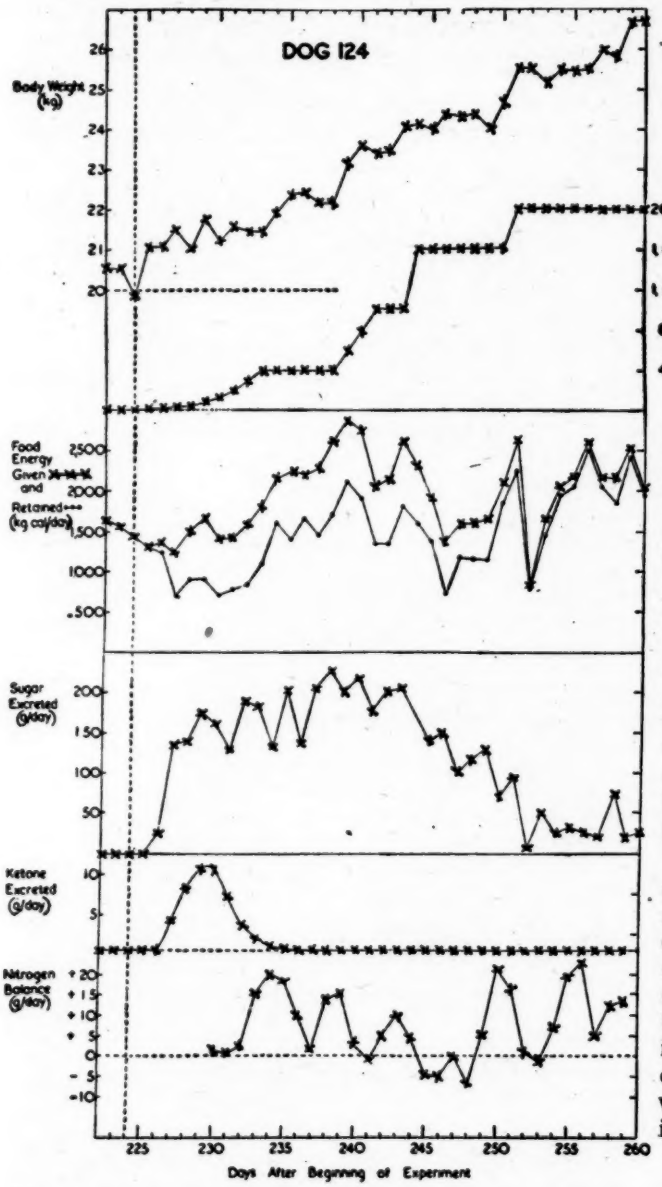

FIG. 1.—Data for dog 124 during the period when protamine-zinc insulin and diabetogenic anterior pituitary extract were given daily simultaneously. The injections were begun on day 223, which is indicated by the vertical dotted line. The dose of extract (5 ml. per day—approximately equivalent to 30 mg. growth hormone per day) was that which induced growth without diabetes during the first 19 weeks of continuous daily treatment. The food intake was unlimited through the experiment.

diabetic the growth response to the pituitary treatment diminished *pari passu* with the development of the diabetic condition, and ultimately the animals stopped growing or even began to lose weight. In these animals further growth could then be induced by the administration of insulin simultaneously with the pituitary extracts (Figs. 1 and 2), although the amount of insulin needed was very large indeed (Fig. 1). We may have here a counterpart to the cases of insulin-resistant diabetes occasionally met with in human beings.

It was clear from these experiments that the diabetogenic action of growth hormone could be converted to a growth-promoting one in the dog if enough insulin were administered with the pituitary extract. This raises two important questions: (1) Does treatment with growth hormone normally induce an enhanced rate of secretion of insulin by the pancreas? (2) Were the pancreases of the treated puppies, during the period before the appearance of the diabetes, secreting an excessive amount of insulin as a requirement for the exhibition of growth at this stage of the experiment? There is much evidence in support of an affirmative answer to the first question (e.g., Milman and Russell, 1949). It may be that under the influence of anterior pituitary growth hormone a fall in the concentration of insulin in the blood occurs, without a corresponding rise of blood-sugar level, and that this fall provides a stimulus for further secretion of insulin by the pancreas. The answer to the second question is probably also positive, although the alterations in carbohydrate metabolism which occur as the young animal grows are still little known (cf. Langfeldt, 1920), and changes in the activity or reactivity of enzyme systems as age advances may be of greater significance than alterations in the rate at which a hormone such as insulin is secreted.

The general conclusion to be drawn from these observations is that the diabetogenic action of growth hormone is regularly demonstrable only in certain adult carnivorous animals, and that in the young of even these species growth rather than diabetogenesis occurs in response to treatment with growth hormone. The association of acromegaly with diabetes, and the finding of Priscilla White that diabetic children are often overheight, are observations in good agreement with this general view.

If, then, growth and growth-hormone-induced diabetes are alternative responses to the same general type of metabolic stimulus, it was of interest to know if the diabetogenic action of growth hormone in intact adult animals could be regarded as the result of a growth stimulus which had become abortive in the adult animal because the adult could not grow indefinitely under the influence of the stimulus. For the elucidation of this question the metabolic balance of dogs and cats treated with anterior pituitary growth-promoting extracts was investigated.

Energy Balance in Idiohypophysial Diabetes

It is convenient to define idiohypophysial diabetes as the condition which exists during a period of anterior pituitary treatment (or of naturally occurring pituitary over-activity) in order to distinguish it from metahypophysial diabetes, the condition which persists under suitable conditions after the cessation of excess pituitary activity.

Now, when intact adult cats and dogs are given subcutaneous administrations of growth-promoting anterior pituitary extract daily for a week or more, the initial response, lasting three to five days, is a rise in body weight associated with nitrogen retention; the fasting blood-sugar level usually does not rise during this period, but may show a tendency to fall slightly. After three to five days the blood-sugar level rises and glycosuria, sometimes accompanied by ketonuria, appears. At this time the upward trend of the weight curve diminishes or subsides, though the retention of nitrogen continues. One effect of growth-hormone administration is an increase in the appetite, and the rise in food intake contributes to the elevation of the body weight. Nevertheless, the rises in body weight and nitrogen retention

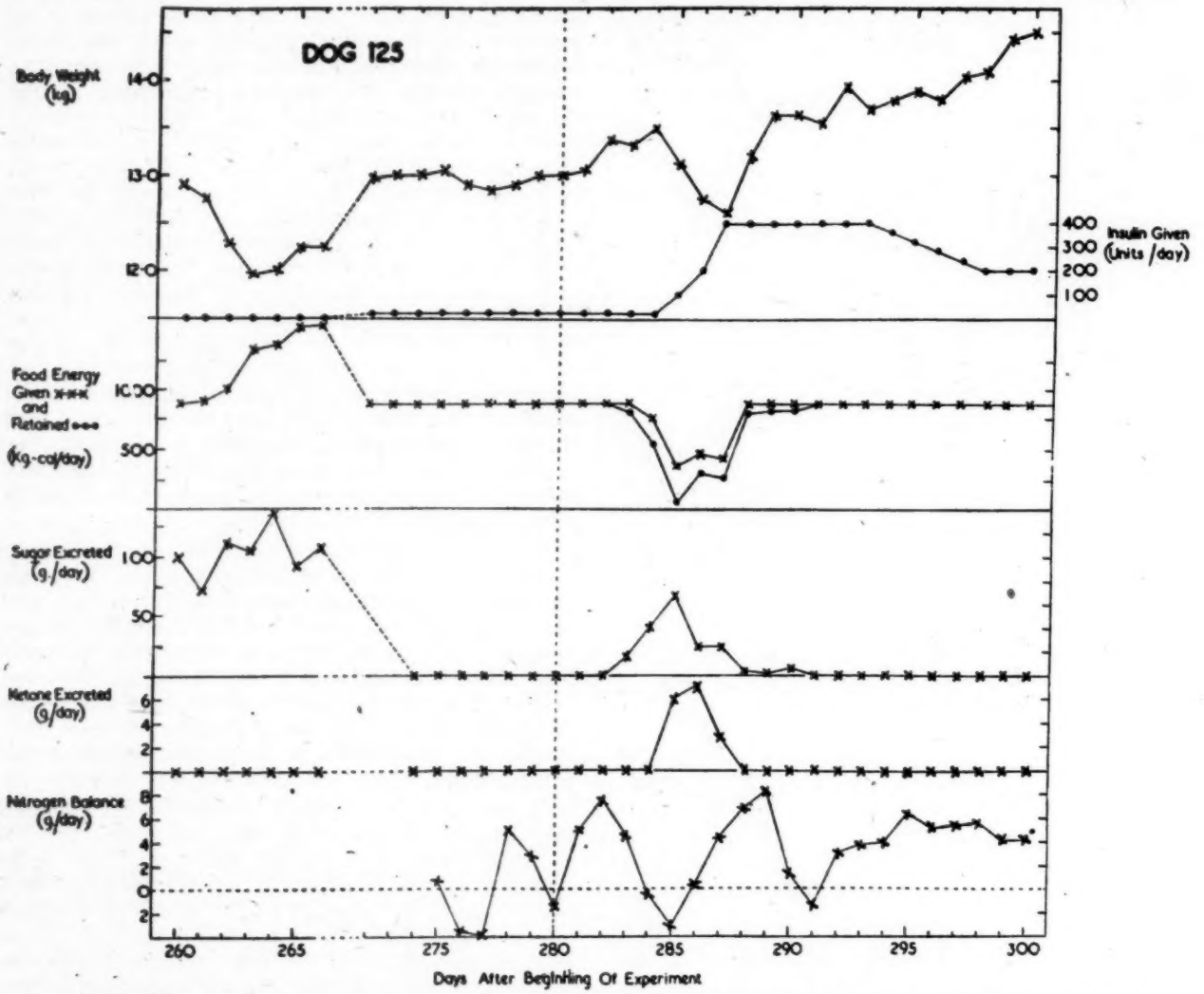

FIG. 2.—The influence of protamine-zinc insulin plus diabetogenic pituitary extract (5 ml. per day—approximately equivalent to 30 mg. per day of growth hormone) on dog 125. The daily injections were begun on day 280, which is indicated by the vertical dotted line. The food intake was controlled from day 270 onwards.

are observed even if the animals receive daily throughout the experiment a constant amount of food sufficient just to maintain a steady body weight before pituitary treatment begins (Young, 1945). Similar observations with respect to nitrogen retention were made with dogs receiving insulin as well as anterior pituitary extract when the food intake was unlimited (Fig. 1), or when the food intake was constant throughout the experiment (Fig. 2).

In all these instances analysis of the tissues of the liver and muscle showed that these were essentially normal in composition, and it appeared that the rise in body weight was associated with a deposition in the body of protein-containing tissue of the composition of muscle, although in some instances the amount of nitrogen retained was more than could be accounted for by the rise in body weight observed (Young, 1945). In intact rats treatment with the same diabetogenic extract did not, of course, induce diabetes but growth only, this growth being associated with a retention of nitrogen even though the food intake was kept constant (Young, 1945; see also Lee and Schaffer, 1934). In the rat the rise in body weight was associated with an increase in the weight of many but by no means all of the skeletal muscles (Greenbaum and Young, 1950).

Direct analysis of the carcasses of the treated rats showed that the deposition of protein-containing tissue was accompanied by a loss of fat, and similar conclusions were drawn from the results of the experiments with dogs and cats (Young, 1945). The energy balance of dogs and rats, treated with anterior pituitary extract alone during an experiment involving a constant daily food intake throughout, is indicated in Fig. 3. Similar data for dog 124, which received insulin simultaneously with the pituitary extract and whose food intake was unlimited, are illustrated in Fig. 4, together with results for dog 125, which was given insulin together with the pituitary extract but whose food intake was limited to that just sufficient to maintain constant body weight, with appropriate insulin treatment before the daily administration of anterior pituitary extract was begun.

It will be seen that the combustion of extra fat contributed additional energy at a time when energy was being lost by the deposition of new protein-containing tissue, and, in the experiments with the dogs, by the excretion of sugar in the urine. The rise of body weight in the experiments with a constant food intake throughout was to be attributed to the fact that approximately 9 kg. cal. of energy is provided by the oxidation of

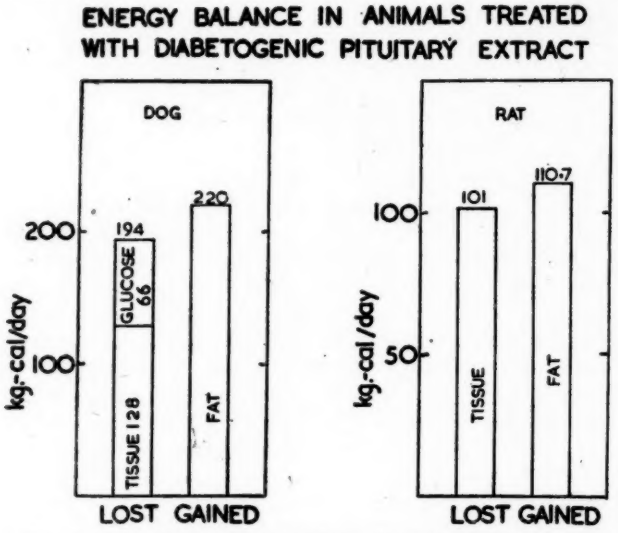

FIG. 3.—The data are mean values—for one week in the case of the dog and for nine weeks in the case of the rat. The food intake was constant throughout the experiment and was just sufficient to maintain a constant body weight before the experiment began. The dogs were normal intact animals.

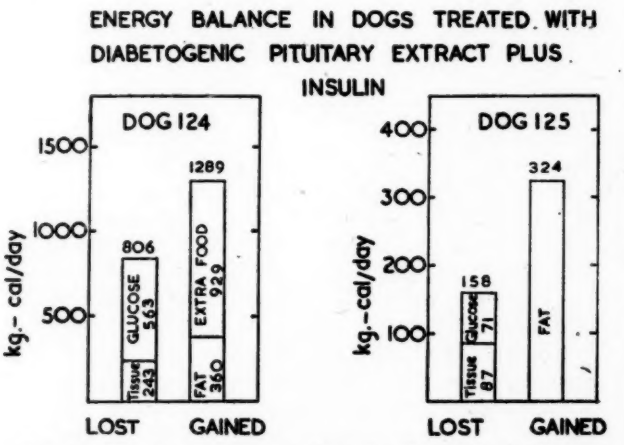

FIG. 4.—The data are mean values—for five weeks in the case of dog 124 and for nearly three weeks in the case of dog 125. The food intake of dog 124 was unlimited (see Fig. 1), while that for dog 125 was controlled (see Fig. 2).

1 g. of depot fat, while little more than 1 kg. cal. of energy is lost when 1 g. of muscle tissue, containing 70% of water, is oxidized. Thus under isocaloric conditions the body weight could rise by nearly 8 g. for each 1 g. of depot fat oxidized. A comparison of the balance sheet for dog 124, whose food intake was unlimited, with that for dog 125, whose food intake was kept constant throughout the experiment, is given in Fig. 4.

Treatment with the diabetogenic pituitary extract, together with enough insulin to suppress ketonuria, induced an increase in appetite of such magnitude that the calories from the extra food consumed were more than sufficient to cover the loss of energy resulting from the excretion of glucose and deposition of new tissue induced by treatment with the extract. In some instances it appears that the rise of appetite induced by the administration of growth hormone may be sufficient to induce a deposition of fat quantitatively greater than the extra loss due to the enhanced rate of fat oxidation, with the result that the animal may deposit protein and fat simultaneously.

The overweightness of the majority of human beings who developed diabetes is well recognized. The possibility that this excessive weight might result from a long-standing oversecretion of pituitary growth hormone, too small overtly to induce the skeletal changes and other stigmata of acromegaly, is an attractive one. In the human being the rise in appetite which would be expected to follow hypersecretion of growth hormone might well compensate, or more than compensate, for the increased rate of oxidation of depot fat. It follows, therefore, that if the overweightness of human prediabetics was the result of pituitary hypersecretion the excess weight would not be ascribable to adiposity alone, but would depend in part upon the deposition of protein-containing tissues. Now the deposition of extra protein-containing tissues tends to raise the specific gravity of the body as a whole (Behnke *et al.*, 1942 ; Young, 1945), and the possibility that the determination of the specific gravity of patients suffering from overweightness might lead to findings of significance, particularly with respect to the aetiology of diabetes, is one for serious consideration.

Antagonism between Insulin and Growth Hormone

The possibility that human diabetes may result from an antagonism between insulin and growth hormone emphasizes the importance of the views of C. F. and G. T. Cori concerning the opposing influence of these two hormones with respect to the activity of the enzyme hexokinase. This enzyme, catalyses the formation of glucose-6-phosphoric acid from glucose and adenosine triphosphoric acid (A.T.P.), and it may well be that the formation of glucose-6-phosphate under the influence of hexokinase constitutes an obligatory initial step in the utilization of glucose for metabolic purposes in general in the animal body.

As was first demonstrated by Gemmill (1940), the isolated diaphragm of the rat will take up glucose from the surrounding medium, and the rate of uptake is enhanced by the addition of insulin to the system *in vitro*. It may be that the limiting factor with respect to the uptake of glucose by the muscle of the diaphragm under these conditions is the activity of its hexokinase system, and that insulin is indeed capable of increasing the activity of the hexokinase *in vitro*, although such is not the only possible interpretation of the observed results. C. F. Cori, however, does believe that under suitable conditions the rate of glucose uptake by rat diaphragm *in vitro* is a safe index of the hexokinase activity of the muscle ; and if this assumption is correct the findings of the Coris and others support the view that insulin enhances hexokinase activity while growth hormone depresses it.

I should like to mention the possibility that growth hormone is not acting directly on the hexokinase but influencing the activity of this enzyme by indirect means. This could be so if two enzymes were concerned, these two competing for a limited amount of A.T.P. at the cell surface. The activity of one of these enzymes, hexokinase, would be enhanced by the presence of insulin, while that activity of the others concerned with the transfer of amino-acids across the cell membrane might be enhanced in the presence of growth hormone. The possibility that certain adrenal steroids catalyse the utilization of A.T.P. for other translocatory processes —for example, those involving cations—might also be considered.

Metahypophysial Diabetes

Metahypophysial diabetes persists, in the intact dog and cat, after the cessation of a short period of pituitary treatment (Young, 1937, 1948), and its persistence is almost certainly to be ascribed to the lesions which are found in the islets of Langerhans in such instances. The existence of metahypophysial diabetes in animals indicates the possibility that in the human being a short period of pituitary hyperactivity with respect to growth-hormone secretion could result in permanent damage to the islets of Langerhans of the pancreas and thus induce a persistingly diabetic condition. Such a metahypophysial diabetes would not be of an insulin-insensitive type if the hyperactivity of the pituitary gland subsided completely, and indeed would find its direct though not primary origin in the pancreatic lesions alone.

Influence of Growth Hormone on Milk Production

Although it may seem at first strange that milk production is to be considered in a discussion of diabetes it is hoped that the reason for this will quickly become apparent. In 1938 Dr. S. J. Folley and I found that the galactopoietic activity (that is, the ability to enhance the milk yield of animals already secreting milk) of anterior pituitary extracts in the cow paralleled their diabetogenic activity in the dog (Folley and Young, 1938), and more recently we have shown that purified growth hormone is highly galactopoietic in cows in declining lactation (Cotes, Crichton, Folley, and Young, 1949). Neither prolactin nor adrenocorticotropin is galactopoietic under the conditions of our experiments, though these hormones may be of importance in the *initiation* of lactation. We believe that it is necessary, in this connexion, to distinguish clearly between the initiation of lactation and the stimulation of an existing milk flow.

Since growth hormone was found to be galactopoietic it was of interest to know how far the treatment of lactating rats with growth-promoting anterior pituitary extract would stimulate the growth rate of the mothers, and how far it would enhance the flow of milk and thus indirectly stimulate the growth of the offspring. The results in Table II show that the *gross* increase

TABLE II.—*Influence of Growth-promoting Anterior Pituitary Extract on the Growth of Nursing Rats and Their Litters (The Figures are Mean Results for Groups of 10 Rats Treated Daily for 14 Days)*

	Nursing Rats		Normal Female Rats	
	Saline-treated	Pituitary-treated	Saline-treated	Pituitary-treated
(*a*) Mothers:				
Initial weight (g.) ..	222	230	221	220
Final weight (g.)	235	271	222	263
Increase (g.)	13	41	1	43
Net increase (g.)	—	28	—	42
(*b*) Young:				
No. in litter	6·3	6·9		
Final weight of young (g.)	27·9	28·4		

in the weight of pituitary-treated mothers is about the same as that of pituitary-treated non-lactating female rats; but, since the control lactating rats rose significantly in weight while the control non-lactating rats did not, the *net* increase in weight of the pituitary-treated lactating rats was less than that of the treated non-lactating animals. The sucklings of the pituitary-treated mothers were not significantly heavier than those of the control mothers at the end of this experiment, and thus there was no evidence of a galactopoietic effect of the extract under these conditions. One might say that when exogenous growth hormone was administered the growth of the mother took precedence over the secretion of extra milk under these conditions.

We have known for many years that pregnant or lactating dogs or cats do not become diabetic when given doses of diabetogenic anterior pituitary extract which are highly effective in inducing diabetes in normal cats or dogs; in fact, one of my earliest failures to produce diabetes with a potent anterior pituitary extract was that of a pregnant bitch (Young, 1938). It would be of great interest to know whether, in such animals, the growth stimulus is confined to the mothers or shared with the offspring, but our present data are insufficient to allow us to draw a definite conclusion on this point so far as the dog and the cat are concerned. For the rat, on the other hand, relevant observations have long been present in the literature. Thus Watts (1935) observed that the treatment of pregnant rats with certain partially purified preparations of the anterior pituitary growth hormone could induce not only a rise in the body weight of the mothers over that of control animals but also a statistically significant increase in the weight of the offspring. This excessive weight of the young from treated mothers was observed in animals for which the gestation time had not been prolonged by the treatment, although in some of Watts's experiments, and also in many of those of others, treatment with some preparations of growth hormone did induce a prolongation of pregnancy in the rat. Such a prolongation can be legitimately ascribed to contamination of the admittedly impure growth hormone with gonadotropins, and was not seen with more purified preparations of the growth hormone.

Cole and Hart (1938) observed that in the rat normal pregnancy stimulates the growth of the body of the mother, and that this extra weight was not completely lost either during lactation or subsequently. In our own experiments untreated lactating rats appeared to show, during the period of lactation, a significantly greater growth rate than did control non-lactating female rats (Table II), and this observation may be indicative of an enhanced secretion of growth hormone during the period of lactation. Our evidence, together with that of Watts (1935) and of Cole and Hart (1938), is in agreement with the view that during both pregnancy and lactation there is an enhancement of the rate of secretion of growth hormone by the anterior pituitary gland, at least in the rat.

With the identification of the growth hormone as an important diabetogenic agent the above considerations are possibly relevant to the observation of Miller, Hurwitz, and Kuder (1944), which has been adequately confirmed, that the tendency to produce large babies, and the high incidence of foetal mortality, found in diabetic women may often be present many years before diagnosable diabetes develops. If an enhanced secretion of growth hormone by the anterior pituitary gland is a factor of importance in the stimulation of foetal growth, and also, after parturition, in the stimulation of milk production, then excessive secretion of growth hormone, beyond the capacity of the tissues to respond adequately, might lead to diabetes as the pathological result of an overstimulated physiological process. It is of interest

to recall the classical experiments of Paul Bert in 1884 in which mastectomy of a pregnant goat led, at parturition, to the transitory appearance of a diabetic condition. Here the removal of the means whereby the physiological process could realize itself led to the pathological condition of a temporary diabetes.

If, in diabetic women, the large babies are to be ascribed to the action of an excessive secretion of growth hormone, I would suggest that the accidents of pregnancy in such women are more likely to be the result of other factors—perhaps an abnormality of secretion of pituitary gonadotropins

Conclusion

In a paper published some years ago (Young, 1947) I wrote: "Growth, including foetal growth, and milk production are processes requiring a special type of metabolic control in that they both necessitate the preservation from oxidization of foodstuff that would otherwise, in an animal in equilibrium, be oxidized. . . Since growth, galactopoiesis, and diabetogenesis all involve a restraint on oxidative processes, it would not be surprising if there were some relationship between the hormonal mechanisms concerned with the control of these phenomena."

The evidence now at our disposal allows us to associate growth, including foetal growth, and milk production as phenomena whose development is stimulated by growth hormone. Excessive pressure on these processes in circumstances where the physiological stimulus cannot fully or properly realize itself can lead to the pathological outcome of diabetes, a condition in which the material preserved from oxidation but not utilized may be excreted in the form of sugar. In the human being a slightly excessive rate of secretion of growth hormone, insufficient to cause overt signs of acromegaly but lasting a long time, might lead to a prolonged but not excessive restraint upon the processes of carbohydrate and protein catabolism and oxidation, combined with the increase in appetite characteristic of growth-hormone activity, so that diabetes ultimately develops. In growth hormone we have a substance that may well be of importance in the aetiology of a serious proportion of cases of human diabetes mellitus.

I wish to express my thanks to the Medical Research Council for their continued support of my researches upon experimental diabetes.

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HYALURONIDASE SKIN SPREADING EFFECT*

AN ANALYSIS OF REPEATED MEASUREMENTS

BY

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Hyaluronic acid has been demonstrated in man in the skin, umbilical cord, synovial fluid, vitreous humour, and some mesenchymal tumours. Its presence is inferred in connective tissue (Wis'ocki, Bunting, and Dempsey, 1947) on histological evidence and by observation of the effect of hyaluronidase. This enzyme system, found in some bacteria and in testicular extract, reduces the viscosity of, and hydrolyses, hyaluronic acid (Meyer *et al.*, 1937, 1940). The possible role of hyaluronic acid and hyaluronidase in connective-tissue diseases has been the subject of wide interest. Guerra (1946a, 1946b) claimed that the skin of patients with acute rheumatism gave enhanced spreading with the enzyme, and, further, that administration of salicylates inhibited this spread. Subsequently reported work (Harris and Friedman, 1949; Jaworski *et al.*, 1950) has not confirmed increased spreading in rheumatic fever, while recent work on the effect of salicylates gives conflicting results. Most reports agree that, *in vitro*, high concentrations are necessary to inhibit hyaluronidase; but while inhibition in therapeutic doses *in vivo* has been confirmed by some workers (Meyer, 1947; Dorfman *et al.*, 1947) it is denied by others (Swyer, 1948; Jones, 1950). Recent American literature (Symposium, 1950) favours the view that salicylates are inhibitory *in vivo*, but does not confirm the enhanced effect of spreading factor in rheumatic fever.

The well-known ability of haemolytic streptococci to form hyaluronidase (Meyer *et al.*, 1940; McClean, 1941; Crowley, 1944; Pike, 1948) has focused interest on the bacteriological relationship of this enzyme to rheumatic fever; the introduction of A.C.T.H. and cortisone, with their observed effect on connective tissue, redirects attention to the substrate and its place in the aetiology of this group of diseases. Preliminary reports indicate that in animals (Opsahl, 1949; Winter and Flataker, 1950) and in man (Shuman and Finestone, 1950) administration of these hormones causes decreased

*Based on a paper read at the Medical Research Society on July 6, 1951.

skin spread with hyaluronidase, and that local intra-articular cortisone increases the viscosity of joint fluid in rheumatoid arthritis (Bywaters and Dixon, 1951).

It seemed that there was no critical analysis of skin spread applicable to clinical research, although adequate investigations have been made on animals (Humphrey, 1943). The present work attempts to evaluate a suitable clinical method for detecting quantitative changes in skin response to hyaluronidase over a period of weeks, and describes some results in rheumatic patients undergoing hormone or salicylate treatment. A subsequent paper will describe investigations of the rate of reconstitution of the skin hyaluronic acid following enzyme treatment. Throughout the investigation bovine testicular hyaluronidase was used.*

Preliminary Investigations

The objects of this investigation were: (*a*) to establish a method of measuring spreading action in the skin repeatedly over a number of days or weeks and to estimate its variability; and (*b*) to observe the response in acute rheumatic fever, and note the effects of hormone or other therapy.

Indicator of Spread

Many substances have been suggested as indicators of degree of spread, but a number of them inhibit hyaluronidase, and this severely limits the choice among dyes and coloured substances. Indian ink, Congo red (0.1% and 0.01%) and Evans blue (0.1% and 0.01%) all produced prolonged or permanent skin staining; various blood pigment derivatives (Fulton *et al.*, 1948) and haematin inhibited hyaluronidase. It has been suggested (Shuman and Finestone, 1950) that *fluorescein* may be used as an indicator by observing under a Wood's lamp the "disappearance-time" of fluorescence in the skin following intradermal injection with the enzyme; but clinically the test was too time-consuming and laborious. Furthermore, it was shown† that a 2.5% solution of fluorescein completely inhibited hyaluronidase, although the concentration used in the test (1/50,000) appeared not to affect the enzyme *in vitro*.

Indigo carmine (0.5% in isotonic PO_4-buffered saline, *p*H 7.2) was painless on injection, gave a clearly defined blue stain capable of accurate measurement, and disappeared within three days. Viscosimetric determinations† of its hyaluronidase inhibitory activity, however, showed that it caused 72% inhibition of a standard hyaluronidase solution within five minutes of mixing. Although the remaining activity caused measurable spread, this was a variable factor, and an analysis of variance of the measure of spread in tests on three individuals on three days each showed a significant component of variation due to differences in test procedure.

Haemoglobin.—Although haemoglobin solution has been widely used in animals and man as a spreading indicator (Madinaveitia, 1938; Humphrey, 1943; Harris and Friedman, 1949; Jones, 1950) its use in repeated skin tests in man seemed not without danger of producing sensitization to blood-group substances. The likelihood of this was minimized by using Group O rhesus-negative blood as a source, although this limited available supplies. Viscosimetric estimations† showed that it had no effect on hyaluronidase activity, and the skin stain disappeared in two to four days. In the absence of a more easily prepared indicator, haemoglobin was adopted and proved satisfactory in use.

*Supplied by Benger's Ltd., Research Department.
†Performed by Benger's Ltd., Research Department.

Method for "Spreading Test"

General.—The flexor forearm skin was used in all subjects. Superficial veins were avoided so far as was possible, because the indicator tended to spread along them, with resultant irregular areas of stained skin, making accurate measurement difficult. All-glass siliconed Mantoux syringes (Luer) with short-bevelled 26 B.W.G. needles were used, and large batches of enzyme and indicator avoided changes of test solutions.

Indicator Solution.—Sterile isotonic human haemoglobin solution with a *p*H of 7.2 was prepared from Group O rhesus-negative blood by lysing packed red cells with an equal volume of distilled water and carefully dissolving in the resulting haemoglobin solution a mixture of 1.65 g. % of $Na_2HPO_4.12H_2O$ and 0.103 g. % of KH_2PO_4. The solution was run through a clarifying filter to remove stroma and then through a sterilizing pad. It was stored at 4°C., and remained stable for several weeks. The haemoglobin content of this product was 12.4 g. %.

Enzyme.—Bovine testicular hyaluronidase in the form of a dried commercial preparation ("hyalase") containing 1,000 "Benger units" per ampoule.

Intradermal injections.—The contents of 1 ampoule of desiccated hyalase dissolved in 1 ml. of indicator constituted the test solution, whereas the haemoglobin alone acted as the control. Attention was paid to the mechanics of intradermal injection (Hechter, 1947); all the injections were performed by the same observer to ensure, so far as was possible, that exact volumes and comparable plunger pressures were used. Siliconed syringes facilitated smooth plunger action with the rather sticky haemoglobin solution.

Dose and Measurement.—The test and control solutions, 0.1 ml. of each, were injected intradermally. Maximum and minimum diameters were measured to the nearest millimetre with needle-pointed callipers, and their product was multiplied by $\pi/4$. This gave the area of the ellipse in square millimetres. Readings

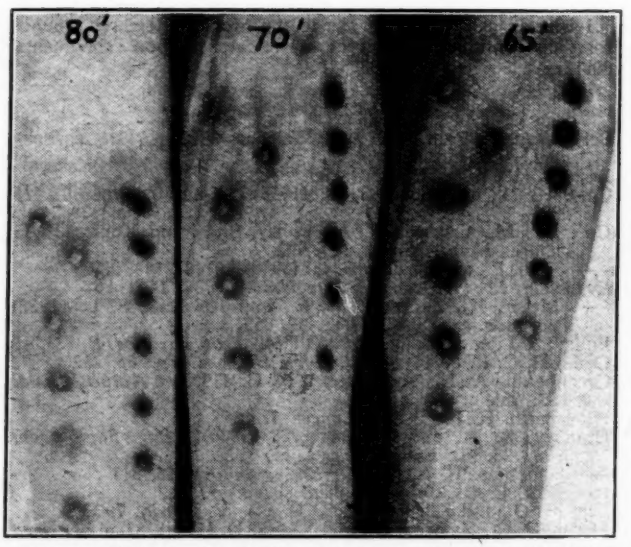

FIG. 1.—Eighteen "spreading tests" on three normal adults 65, 70, and 80 minutes after injection. Tests on inner (L.) and controls on outer (R.) aspects of forearms.

repeated at 30 and 60 minutes showed a difference in spread, but the stained area was more clearly defined at the end of one hour (see Fig. 1). The purpose of this investigation was to measure gross differences in spreading in patients on various therapeutic regimes. In testing fairly large numbers of patients it was not practicable to measure spreading areas after only, say, five minutes, as advocated by Hechter (1950). Readings were therefore made at one hour, in agreement with the practice of other clinical workers (Harris and Friedman, 1949; Jones, 1950), and the degree of spread expressed as the "spreading ratio" (test/control ratio, or T/C ratio).

The first experiment was designed to discover whether there was a significant difference between skin sites on the same day or between repeated tests on different days.

Experiment 1

Three normal adult subjects (two male and one female) had six test and six control injections into the flexor skin of one forearm, the medial side being used for the test and the lateral side for the control injections (Fig. 1). This procedure was repeated on four different days, alternate forearms being used, allowing an interval of two to five days between tests and hence adequate time for reconstitution of the hyaluronic acid depolymerized by the previous enzyme injections. On each day identical solutions were used, fresh enzyme was dissolved, and the injections were performed and measurements made by the same observer (E. J. H.).

Results.—Two of the three subjects showed sensitization (flare with or without wheal) to the enzyme preparation during repetition of tests. They were therefore excluded, and the subject not exhibiting sensitivity gave the results shown in Table I—which shows that variation

TABLE I.—*Experiment 1. Day-to-day Variation in Spreading Test*

Spreading (T/C) Ratio in 6 Tests Repeated on 4 Days in One Subject

Skin Site	1st Day	2nd Day	3rd Day	4th Day
1	1·96	2·66	1·54	2·70
2	1·87	2·58	1·91	2·00
3	1·95	2·65	2·65	2·23
4	1·95	2·33	1·98	2·17
5	2·07	2·28	1·73	2·10
6	1·88	2·56	1·79	1·75

Total degrees of freedom = 23.

Analysis of Variance

Item	Sum of Squares	n	Mean Sq.	Variance Ratio	P
Sites	0·3794	5	0·0759	1·14	Not significant
Days	1·3037	3	0·4344	6·48	0·01
Error	1·0080	15	0·0672	—	
	2·6911				

in spreading ratios on different days was not due to differences in spreading between skin sites. Thus one pair of injections sufficed on any part of the flexor forearm skin.

Experiment 2

This experiment was made to determine the range of variation from day to day. Six normal adults (four male and two female) had one pair of injections on each of four different days. Identical preparations were used for all subjects on each day, and the injections performed and measurements were made by one observer (E. J. H.).

Results.—Two subjects showed sensitivity during repetition of the tests and were therefore excluded from analysis of the results given in Table II, which shows

TABLE II.—*Experiment 2. Measurement of Day-to-day Variation*

Spreading (T/C) Ratio in 4 Normal Adults Tested on 4 Different Days

Subject	1st Day	2nd Day	3rd Day	4th Day
G.L. ..	2·92	2·01	2·15	2·77
M.S. ..	1·37	2·04	2·37	1·65
L.G. ..	2·94	2·17	2·04	2·17
R.C. ..	2·00	1·96	2·52	2·64

Analysis of Variance. Total No. of Tests, 16

Item	Sum of Squares	n	Mean Sq.	Variance Ratio	P
Individuals ..	0·8211	3	0·2737	1·14	Not significant
Days	0·1912	3	0·0637	—	" "
Error	1·8672	9	0·2075	—	" "
	2·8795	15			

Variance = 0·191967. Mean = 2·23. S.E. = 0·45. Variance of mean = 0·011997.

that: (1) day-to-day variation is due to individual characteristics and not to variations in technique; (2) differences observed between individuals are not significantly greater than day-to-day variation in single individuals; and (3) the coefficient of variation is about 20%.

Experiment 3

This experiment was made for the purpose of observing the range and mean spreading ratio in a group of rheumatic fever cases. Initial and acquired hypersensitivity to the enzyme preparation presented a considerable difficulty in the interpretation of readings, and is discussed below. To exclude hypersensitivity effects in the estimate of range and mean in rheumatic fever subjects, readings in this experiment were taken only from subjects undergoing their first enzyme (spreading) test, and cases showing wheal, flare, or indefinite margin of spread area were excluded. Twenty-one cases of acute rheumatism gave tests satisfying these criteria; in all there was a recent history of arthritis and signs of active carditis with raised E.S.R. The results are shown in Table III, and are compared with normal subjects in Table IV. It will be seen that the normal mean is 2.23,

TABLE III.—*Experiment 3. Spreading Test in Acute Rheumatic Fever. Spreading (T/C) Ratio in 21 Cases of Acute Rheumatic Fever (One Test Only on Each Case)*

2·08	2·65	1·85	1·62	1·96	1·98	2·38
1·71	1·42	1·65	1·49	1·53	1·61	2·61
2·36	2·80	2·60	2·56	2·08	1·81	2·72

Variance = 0·209580. Mean = 2·07. S.E. = 0·46. Variance of mean = 0·009980.

TABLE IV.—*Comparison of Results in Normal Subjects (Experiment 2) and in Cases of Acute Rheumatic Fever (Experiment 3)*

Experiment 2 ..	Mean, 2·23	Variance of mean,	0·011997
" 3 ..	" 2·07	" " "	0·009980
	Difference, 0·17	Sum,	0·021977

S.E. of difference = 0·148
c = 1·15. P = 0·25. (n = >30)

the rheumatic mean 2.07, and the S.E. of their difference is 0.148; the difference in this comparison is therefore not significant, which does not support Guerra's claim that skin spread is enhanced in patients with acute rheumatism.

Development of Hypersensitivity

Sherwood Jones (1950) reported a high incidence of initial allergic reactions in both normal and rheumatic fever subjects. In the present investigation a somewhat purer enzyme preparation was used, and immediate local reactions were fewer, although, as shown in Table V, eventually all patients became sensitized; this sensitivity may probably be ascribed to protein impurity in the enzyme preparation. Non-specific serum inhibitor was not measured in this study.

TABLE V.—*Hypersensitivity in "Spreading Test"*

No. of Tests Before Sensitivity Acquired	No. of Cases (Both Sexes and All Ages)			Total No. of Cases	Total No. of Tests	Final Grade of Sensitivity	
	R.F.	R.A.	C.D.			No. Cases	Grade
0	11	3	3	17	101	7 10	1 2
1	7	2	—	9	77	4 5	1 2
1–5	6	1	1	8	85	3 5	1 2
5–10 ..	4	2	—	6	67	4 2	1 2
Over 10 ..	5	1	—	6	110	3 3	1 2
Totals ..	33	9	4	46	440	21 25	1 2

R.F. = Rheumatic fever. R.A. = Rheumatoid arthritis (adults and children). C.D. = Collagen diseases (excluding dermatomyositis).

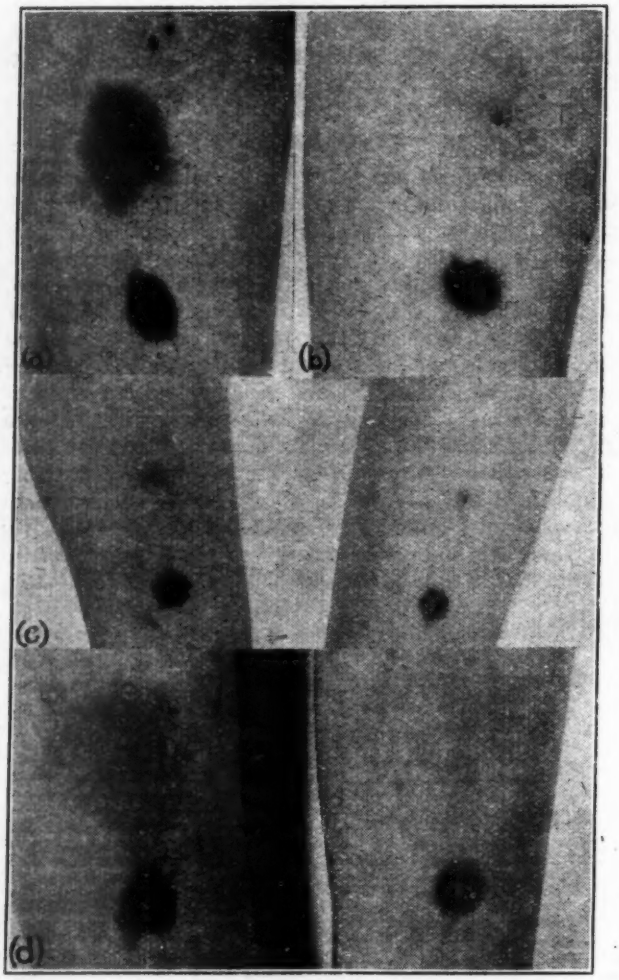

FIG. 2.—(*a*) A "normal" spreading test, the test injection being the same depth of colour as the control, with a small pale central area and a bluish clearly defined rim of pigment. (*b*) Grade 1 hypersensitivity. The test area is large, pale, homogeneous, without a pale central spot, and with an indefinite edge incapable of accurate measurement. (*c*) Grade 2 hypersensitivity. The test injections are invisible owing to complete dispersal of the haemoglobin within the hour. (*d*) Grade 2 hypersensitivity. The test injections show a wheal and flare.

A normal (non-sensitized) reaction consisted of a test injection with the same depth of colour as the control, a small pale central area, and a bluish clearly defined rim of pigment (Fig. 2, a). When sensitivity occurred the test area became large and pale, homogeneous, without a pale central spot, and with an indefinite edge incapable of accurate measurement (Grade 1 sensitivity) (Fig. 2, b). With more marked reaction there was an immediate wheal and flare, or complete dispersal of the indicator within an hour, rendering the test invisible (Grade 2 sensitivity) (Fig. 2, c and d). Allergic dermal oedema potentiates enzyme spread owing to increased intradermal pressure (Hechter, 1947), so it was necessary to determine a spreading ratio value below which spread due to oedema could be reasonably excluded. The criteria of sensitivity described above were used, and a critical value of the spreading ratio of 3 was derived by taking the mean ratio of the 21 non-sensitized cases shown in Table III, and adding twice the standard error of the sample. Thus values larger than 3 were considered unlikely ($P = 0.02$) to occur in rheumatic fever cases without sensitization; and in fact values above 3 were usually associated with definite signs of hypersensitivity.

Table V shows the incidence of hypersensitivity. We tested 33 cases of rheumatic fever, 9 cases of rheumatoid arthritis, and 4 cases of collagen disease. The collagen disease group included 1 case of polyarteritis nodosa, 1 of erythema nodosum, and 2 of disseminated lupus erythematosus. These 46 cases had 440 tests with hyaluronidase and all eventually became sensitized, 21 to Grade 1 sensitivity, and 25 to Grade 2 sensitivity. One-third of these exhibited sensitivity at their first exposure to the substance, others after one injection, and some not until 10 or more tests had been performed. The proportion of hypersensitivity increased with serial testing, as did the degree of sensitivity in the same individual.

Dermatomyositis.—Three cases of dermatomyositis showed a different skin reaction, there being no macroscopic difference between test and control injections. One of these patients died before hypersensitivity developed, but the others eventually became sensitized (Table VI). This suggests that the substrate is altered in this disease, preventing hyaluronidase spread.

TABLE VI.—*"Spreading" Test in Dermatomyositis*

Sex	Age	Total No. Tests	Results
F	8	11	Practically no difference between test and control injections. Died before hypersensitivity occurred
F	13	34	At first no difference between test and control. Then slight difference followed by Grade 2 sensitivity
F	19	8	No difference between test and control followed by Grade 1 sensitivity

Experiment 4: The Effect of Hormone Treatment on the Spreading Test

Acute rheumatic fever cases were allocated at random to one of three treatment groups—salicylate, cortisone, or adrenocorticotrophic hormone (A.C.T.H.). The treatment lasted six weeks, the total hormone dosage for

each patient being fixed at 4.1 g. of cortisone or 1.62 g. of A.C.T.H., irrespective of age or body weight. Salicylate, however, was given as aspirin, 1–4 g. daily, according to body weight. This small dosage did not always control acute arthritis, which sometimes required a supplement of pethidine. Fig. 3 shows the effect of therapy on skin spread, each patient having proved rheumatic activity at the start of treatment. Four spreading tests were done on each case at approximately equally spaced intervals during treatment.

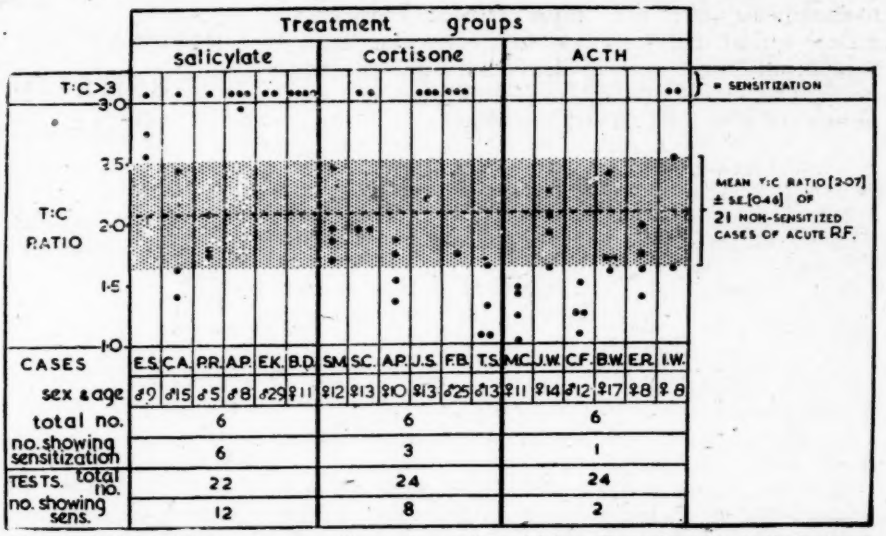

FIG. 3.—Effect of therapy on spreading action and sensitizing effect of bovine testicular hyaluronidase in acute rheumatic fever.

Results.—In the salicylate group the readings either fell within normal range or exhibited sensitivity. Some of the cortisone cases showed inhibition of spread, but only the A.C.T.H. group showed a significant difference, the mean of all the readings lying below the normal range. In the salicylate group 12 out of 22 tests showed hypersensitivity; with cortisone 8 out of 24 and with A.C.T.H. only 2 out of 24 tests showed hypersensitivity during treatment. However, all the A.C.T.H. group showed a marked "release" rise of ratio following cessation of therapy.

Discussion

Haemoglobin was found to be the best of a number of substances tested as spreading indicators, and gave as clear a zone of staining as any of the chemical dyes tested. None of the latter were satisfactory as indicators, mainly because of their inhibitory effect. The tonicity and *p*H of the haemoglobin solution, which profoundly affect the activity of the enzyme (McClean and Hale, 1941; Madinaveitia and Quibell, 1941; McClean, 1943; Hale, 1944), required careful adjustment to avoid pain on injection. The *p*H chosen (7.2) lies within the range allowing hyaluronidase activity.

When the spreading test was used repeatedly in the same patient hypersensitivity always developed, and this proved a serious drawback to the usefulness of the test. It is possible that with purer preparations of bovine hyaluronidase this effect might be delayed or reduced. The incidence of tests showing hypersensitivity in the three groups suggests an inhibitory effect on this phenomenon by A.C.T.H.; although the numbers in each treatment group were small all patients eventually showed hypersensitivity after treatment was stopped, including the A.C.T.H.-treated group. The effect of cortisone on development of hypersensitivity is probably not significant; this is in agreement with Stollerman *et al.* (1951), who found that cortisone therapy did not inhibit the wheal and erythema resulting from union of antigen and sensitizing antibody in the skin of human beings. In the salicylate group development of hypersensitivity was observed in all six cases; but, as already stated, the dosage was rather low.

Even with the exclusion of hypersensitivity effects, the spreading ratio showed considerable variation in one individual from day to day; in studying groups of cases, however, this effect was balanced by the similar variation observed between patients (as shown in Table II), so that the effect on spreading ratio of drugs used in the treatment of groups of cases was discernible by comparison of mean values in different groups. Variation was observed, as described, both between individuals and from day to day in the same individuals. Differences between individuals may be ascribed partly to age and sex (Lurie and Zappasodi, 1939); in children and women, spreading was more clearly defined than in men, and in atrophic inelastic senile skin.

The occurrence of day-to-day variation in an individual was shown to be due to causes other than variation in technique—that is, there was a real individual variation. Environmental conditions may contribute to this, but humoral factors also may be significant. For example, in rabbits oestrogens (Sprunt and McDearman, 1940) inhibit spread, whereas Lurie and Zappasodi (1942) found an opposite effect with luteinizing hormones. With regard to non-specific serum hyaluronidase inhibitor, although this has been shown by Dorfman (1950) to be increased in rheumatic fever, it has also been shown (Dorfman and Moses, 1950) that A.C.T.H. decreases its serum level in this disease. The decreased spreading effect associated with A.C.T.H. described above is therefore unlikely to be due to action by the inhibitor, and may reasonably be ascribed to the action of the hormone. This is in agreement with Hechter (1947), who concluded that serum antihyaluronidases do not significantly affect the spreading activity of the injected enzyme. It is known that A.C.T.H. stimulates the production of a number of corticosteroids, including compound F, and some of these have been shown to be hyaluronidase inhibitors in animals (Opsahl, 1949; Winter and Flataker, 1950). Alternatively, adrenal corticosteroids may alter the substrate in such a way that the spreading effect of hyaluronidase is reduced.

The findings in dermatomyositis are interesting; hyaluronidase seemed to cause no significant spreading effect in the skin of these cases, unless there was also hypersensitivity to the enzyme. In this disease fibrosis and oedema in the skin are possible factors influencing spread. In oedema of renal or cardiac origin we have not found reduced spreading; and in six individuals with new or old scars injection of haemoglobin and

hyaluronidase into scar tissue showed considerably greater spread than haemoglobin alone. Our findings suggest, therefore, that in dermatomyositis the hyaluronic component of the skin is either deficient or is unresponsive to testicular hyaluronidase.

Summary

A method, using haemoglobin as indicator, of measuring the spreading effect of hyaluronidase in the skin on repeated occasions is described and its inherent variability assessed.

This "spreading test" was performed in cases of rheumatic fever, rheumatoid arthritis, and connective-tissue disease.

No significant difference was found in hyaluronidase spread in patients with acute rheumatic fever and in normal subjects.

Hypersensitivity to the enzyme preparation develops readily; this limits the usefulness of the method.

Significant inhibition of spread and of hypersensitivity to hyaluronidase occurs in the skin of rheumatic fever patients under treatment with A.C.T.H.

In dermatomyositis no significant spreading effect was observed with hyaluronidase.

We would like to thank Dr. E. G. L. Bywaters, who suggested this study, and Dr. L. E. Glynn, for constant encouragement and criticism; Dr. Frank Fletcher, of Benger's Research Department, for turbidometric studies and a generous supply of hyalase; Mr. P. J. Fisk for the photographs; normal volunteers for their co-operation; and the Central Syringe Service staff at this hospital, who rendered this investigation possible.

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The Scottish National Blood Transfusion Association announces that in the last 12 months about 55,000 pints of blood were used in Scottish hospitals. There are 10 Scottish donors who have given more than 50 donations, and 102 who have given more than 25 donations.

RECONSTITUTION OF THE DERMAL BARRIER TO DYE SPREAD AFTER HYALURONIDASE INJECTION*

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The spread of material injected into the skin depends upon the state of the ground substance. Hyaluronidases depolymerize and hydrolyse the hyaluronic acid component, with resulting increase in spread. Subsequently the hyaluronic acid is replaced or restored to its original state, and the barrier to spread is reconstituted.

Hechter (1948) has investigated the time taken for reconstitution of this barrier after breakdown by hyaluronidase, using the disappearance time of saline blebs in skin sites previously treated with testicular enzyme; he concluded from results with a range of enzyme concentrations that restoration of the barrier took from 24 to 48 hours in six normal adults. No other work in this field has been found by us. Hechter infers that the replacing substance is identical with the original substrate, since it reacts to a further dose of enzyme in the same manner as untreated skin.

The role of hyaluronic acid in the pathogenesis of rheumatic fever is not known. In the joint fluid from acute rheumatism the viscosity is only slightly decreased, whereas in rheumatoid arthritis defective polymerization of the hyaluronic acid of the synovial fluid is indicated by a well-marked fall in viscosity (Ragan and Meyer, 1949). Furthermore, intra-articular (local) cortisone in this disease causes the secretion of normal (highly polymerized) hyaluronic acid with increase in viscosity of the fluid (Bywaters and Dixon, 1951). However, the histology of rheumatic fever shows abnormal Feulgen staining of the connective tissue in and around lesions; and the present work presents evidence which suggests alteration in the reconstitution rate of skin hyaluronic acid after its breakdown by hyaluronidase in cases of acute rheumatic fever and rheumatoid arthritis and some observations of the effects of A.C.T.H. and cortisone on this abnormal response.

Methods

Skin subjected to hyaluronidase action continues for a time to permit increased spreading of injected material. This has been explained on the hypothesis that the hyaluronic acid depolymerized by the enzyme is itself repolymerized or replaced by more highly polymerized substrate, processes which take time to complete. Serial

*Based on a paper read to the Medical Research Society on July 6, 1951.

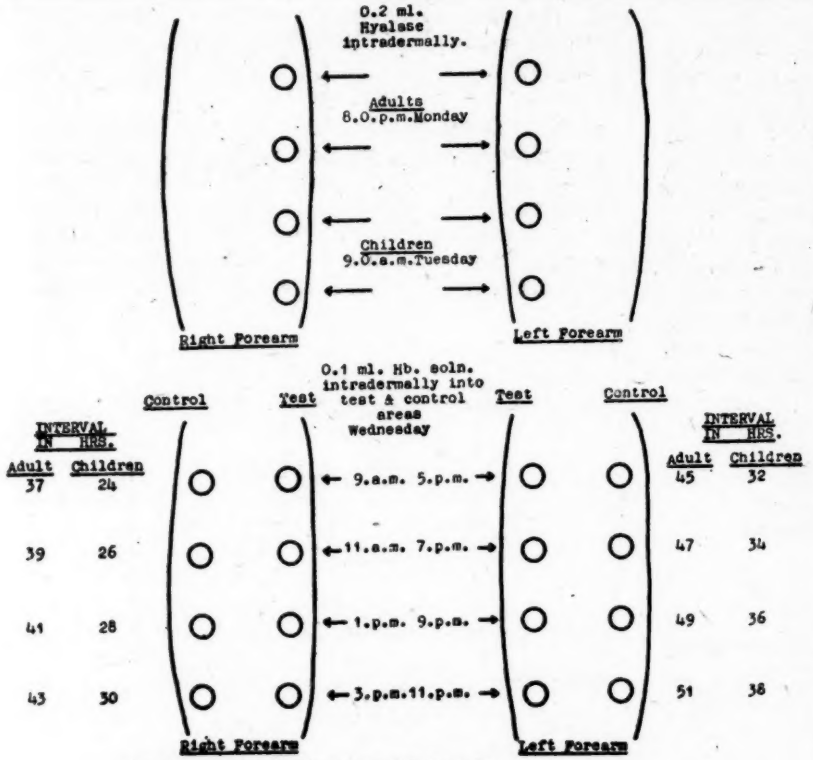

FIG. 1.—Reconstitution time (Method I).

spreading tests in enzyme-treated skin, therefore, will show spread greater than that in normal skin until a sufficient interval has elapsed to allow replacement of highly polymerized ground substance. Comparisons of spread in treated and untreated skin at successive intervals from the enzyme injection will give an estimate of the time necessary for full reconstitution.

The flexor forearm skin was used in all subjects. All-glass siliconed Mantoux syringes (Luer) with short-bevelled 26 B.W.G. needles were used, and large batches of enzyme and indicator avoided frequent changes of test solutions.

Indicator Solution.—Sterile isotonic human haemoglobin solution with a *p*H of 7.2 was prepared from Group O rhesus-negative blood, as described in the previous paper.

Enzyme.—Bovine testicular hyaluronidase as a dried commercial preparation ("hyalase"*).

Method I. Dose and Measurement

An intradermal injection of 0.2 ml. of a standardized hyaluronidase solution (1 ampoule of desiccated hyalase containing 1,000 "Benger units" dissolved in 1 ml. of normal saline) was made into four sites on the inner aspect of each forearm, each site being marked by indelible ink (Fig. 1). Thirty-seven hours after enzyme treatment 0.1 ml. of haemoglobin was injected into the topmost enzyme-prepared site and also into adjacent control skin. One hour after injection the diameters of the spread were measured in test and control areas. At 39 hours a further pair of injections were made, and were measured after one hour, and the process was repeated at two-hourly intervals until the measurements of both areas were the same. In this way the amount of spread of a haemoglobin solution in previously enzyme-treated skin could be compared with the amount of spread in control skin at any predetermined interval of time from the original enzyme injection. In the case of children, somewhat shorter time intervals were used. When the area of spread in the enzyme-treated area failed significantly to exceed the area of spread in the control area it could be concluded that the barrier to spread in the two areas was the same; the skin hyaluronic acid had been fully reconstituted. Maximum and minimum diameters were measured to the nearest millimetre with needle-pointed callipers and their product multiplied by $\pi/4$ to give the area of the stained ellipse.

The area of the spread permitted by the enzyme-treated skin compared with the spread in the control skin gave a "spreading ratio" (test/control ratio, or T/C ratio), which was used in comparing sites to determine the end-point—that is, the reconstitution time (Fig. 2). As there was some unavoidable variation between control spreading areas in the same arm, it was necessary to determine a value for the spreading ratio above which differences in spreading were unlikely to be due to chance variation alone. As shown in Table I, a figure exceeding 1.24 for the spreading ratio was considered significant, and this value was used in determining the end-point.

TABLE I.—*Significance of Spreading Ratio Values in Determining Reconstitution Time*

$$\text{Spreading ratio (T/C ratio)} = \frac{\text{Test (enzyme) area}}{\text{Control area}}$$

100 pairs of control areas measured. The mean ratio of unequal pairs (74 pairs) = 1.1187.

Standard deviation = 0.0770

At P = 0.05 level, values greater than

$1.1187 + 1.64 \times 0.0770 = 1.24$

indicate a significant difference between enzyme-treated and normal skin.

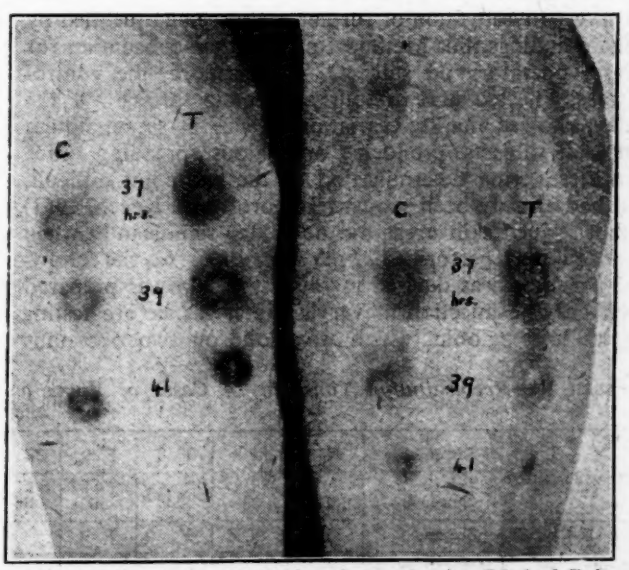

FIG. 2.—Showing reconstitution time end-point (Method I) in two normal adults. At 41 hours both test and control were the same size.

*Batches supplied for this research by Benger's Ltd.

Results with Method I

Experiment 1: Normal Subjects.—Fig. 3 shows the results obtained. A relationship between age and reconstitution time is apparent, the rate of replacement of hyaluronic acid being greater in younger children than in older children and adults. In those of 14 years and under reconstitution was complete by 30 hours, whereas those over 14 took 30–42 hours. The normal range in healthy subjects of all ages lies between 24 and 42 hours. Heat-inactivated hyaluronidase used in the reconstitution test instead of active enzyme gave no greater spread than haemoglobin solution alone. This excluded the enzyme protein content or other non-specific effects as factors responsible for spread.

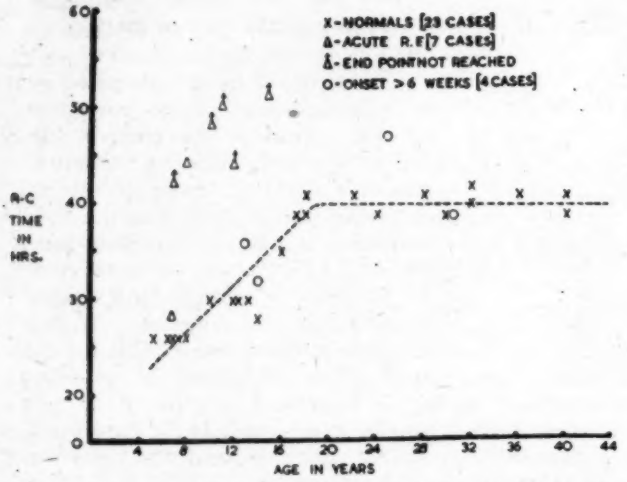

FIG. 3.—Skin reconstitution time (Method I) after treatment with hyaluronidase.

Experiment 2: Rheumatic Fever.—Fig. 3 also shows reconstitution times determined on seven cases of acute rheumatic fever within three weeks of onset and receiving no specific treatment. Six showed a prolonged reconstitution time, twice the normal for their age, or more. Four inactive cases, with onset more than six weeks before testing, gave results falling near the normal curve. Investigation of further cases seemed justified by these findings, but Method I proved time-consuming for both operator and subject. Furthermore, the control areas, injected at two-hourly intervals throughout the day, showed marked variation in size in some though not all subjects, producing anomalous spreading ratios and rendering determination of the end-point difficult. It had already been shown (Holborow and Keech, 1951) that stained skin areas did not differ significantly when several were performed *at the same time*. So the following method was devised in which the skin was prepared by enzyme injection at varying intervals before testing with haemoglobin, which was done on two occasions only. However, the end-point could only be determined within six hours instead of at the two-hourly intervals of Method I.

Method II

In this test the hyaluronidase solution was injected into both forearms, the topmost pair of sites at, say, 9.30 a.m. and the other three pairs at twelve-hourly intervals thereafter (Fig. 4). Forty-eight hours after the first pair of enzyme injections all the sites on the right arm were tested simultaneously with haemoglobin solution, and 54 hours after the first enzyme injections all the sites

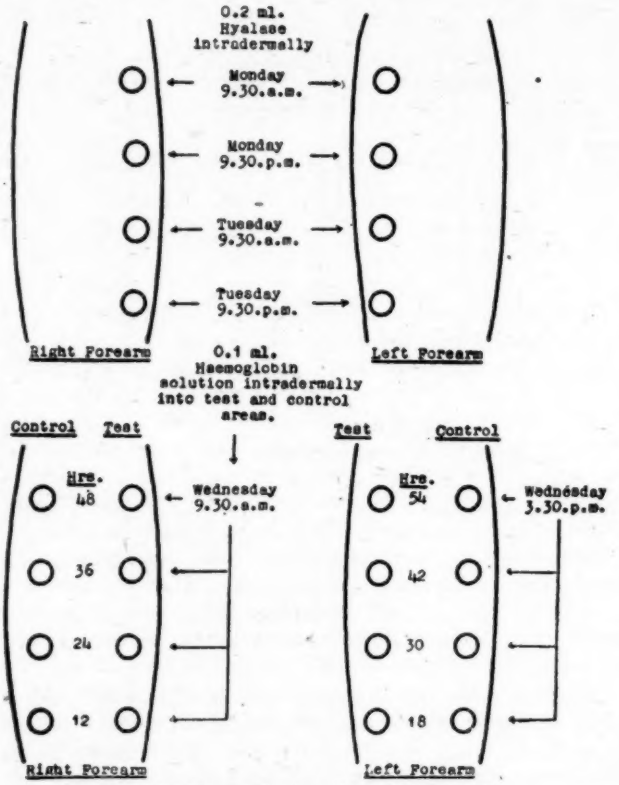

FIG. 4.—Reconstitution time (Method II).

on the left arm were similarly tested; thus a range of observations was obtained from 12 hours to 54 hours, at six-hourly intervals (Fig. 5).

Infra-red photographs were compared with orthochromatic photographs using a red or blue filter. Fig. 6 shows the same pair of arms photographed by both methods; infra-red confirmed that the extent of spread was in fact being measured and that the injection was into the enzyme-treated area, which shows as a definite zone in each test site in both.

Results with Method II

With Method II further rheumatic fever cases were investigated. Twelve acute and 12 convalescent cases were paired according to sex and age, and reconstitution

TABLE II.—*Reconstitution Times in 24 Cases of Acute and Convalescent Rheumatic Fever, Paired According to Sex and Age*

Convalescent	Sex and age:	M 7	M 8	F 8	F 9	M 10	F 11	M 11	F 11	F 12	M 14	F 14	F 17
	Reconstitution time in hours	24	24	24	30	36	36	30	36	30	36	36	36
Acute	Sex and age:	M 6	M 8	F 8	F 9	M 9	F 11	M 12	F 12	F 11	M 15	F 14	F 15
	Reconstitution time in hours	54+	54	54+	54+	54	54+	54+	54+	54+	54+	48	54+

54+ = End-point not reached.

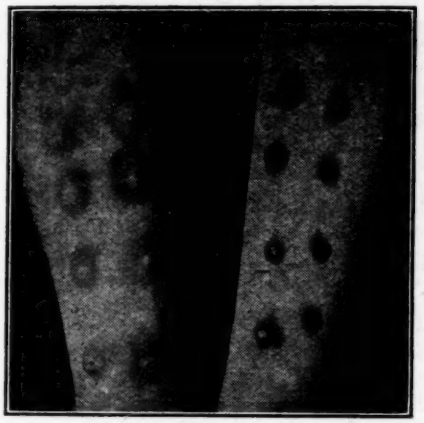

FIG. 5.

FIG. 6.

FIG. 5.—Reconstitution time (Method II) in a child with acute rheumatic fever. Right forearm seven hours and left forearm one hour after injection. The dermal barrier had not reconstituted by 54 hours. FIG. 6.—The same arms photographed with orthochrome and infra-red. The latter confirms that the extent of spread was being measured, and that the injection was into the enzyme-treated area.

times were determined on each pair. As shown in Table II, all the acute cases gave a prolonged reconstitution time; all the convalescent cases gave results falling within the normal range.

Cases of rheumatoid arthritis were next investigated, and similar findings were observed (Table III). In 12 out of 13 active cases of Still's disease the reconstitution times were prolonged above normal, and also in three out of four cases of adult rheumatoid arthritis. In contrast to the findings in rheumatic fever, however, clinical inactivity was not found to be associated with a return to normal reconstitution time. Four cases of clinically inactive Still's disease with normal E.S.R. showed definitely delayed reconstitution. The diagnosis in the other case in this group has since been altered to scleroderma.

TABLE III.—*To Show Prolongation of Reconstitution Time in Both Active and Inactive Rheumatoid Arthritis*

Diagnosis	Sex and Age	E.S.R. (Westergren)	Reconstitution Time in Hours
13 cases of Still's disease (active)	M 7	100	54+
	F 9	35	54
	F 9	113	48+
	M 9	58	54
	M 10	70	48
	M 11	30	54+
	M 11	40	36
	M 11	35	48
	F 11	37	54+
	F 11	54	54+
	M 14	115	54+
	M 14	53(W)	42
	M 14	62	54
5 cases of Still's disease (inactive)	M 5	3	54+
	F 13	5	36*
	M 14	9	54+
	F 16	8	54+
	M 17	15	54
4 cases of rheumatoid arthritis (active)	F 29	86	48
	M 42	40(W)	36
	F 56	116	54+
	M 64	42	48

54+ = End-point not reached. (W) = Wintrobe E.S.R.
* Recent revised diagnosis of scleroderma.

In an attempt to define the specificity of these results for rheumatic disease, reconstitution times were recorded in active cases of pulmonary and/or bone tuberculosis, Table IV shows the results in 19 cases of tuberculosis with raised E.S.R., and in two other non-rheumatic cases. All these gave results within the normal range; in fact, the adults had rather low readings for their age.

TABLE IV.—*To Show Reconstitution Time is Unaffected in Non-rheumatics with a Raised Sedimentation Rate*

Diagnosis	Sex and Age	E.S.R. (Westergren)	Reconstitution Time in Hours
19 cases of active pulmonary and/or bone tuberculosis	M 9	23(W)	36
	F 10	30	24
	F 10	30	30
	F 15	33	36
	M 17	66	36
	M 19	18	36
	F 20	37	36
	M 25	54	36
	M 25	70	36
	M 26	27	36
	F 33	46	36
	M 36	64	24
	M 37	68	30
	M 38	35	36
	F 38	79	30
	F 39	20	24
	M 43	24	30
	F 50	104	36
	F 61	54	36
Osteomyelitis	F 12	36(W)	30
Pneumonitis	F 18	43(W)	42

(W) = Wintrobe E.S.R.

Effects of Hormone Treatment

The reconstitution time of the dermal barrier was measured in acute rheumatic fever before, during, and after therapy (Table V). Three groups of six early

TABLE V.—*Reconstitution Times in 18 Cases of Acute Rheumatic Fever Treated with Salicylate, Cortisone, and A.C.T.H.*

Treatment	Sex and Age	Reconstitution Time in Hours		
		Before Treatment	During Treatment	After Treatment
Salicylate	M 5	54	30	24
	M 8	NR	54+	24
	M 9	54	30	30
	F 11	54+	30	24
	M 15	54	42	30
	M 29	54+	36	(Relapse) 54
Cortisone ..	F 10	54+	WF	30
	F 12	54	24	30
	F 13	NR	30	24
	F 13	NR	54+	24
	M 13	54+	54+	24
	M 25	NR	48	36
A.C.T.H.	F 8	54+	24	24
	F 8	54+	54+	24
	F 11	54+	30	30
	M 12	54+	24	24
	F 14	48	42	36
	F 17	54+	36	30

54+ = End-point not reached. NR = No reading. WF = Wheal and flare.

active cases were treated respectively with salicylate, cortisone, and A.C.T.H. for a period of six weeks. The total dosage was as follows: cortisone, 4.1 g.; A.C.T.H., 1.62 g.; salicylate was given as aspirin in doses of 1–4 g. a day according to body weight. This small dosage of salicylate did not always control acute arthritis, which sometimes required a supplement of pethidine. In four cases readings for reconstitution time could not be obtained before starting treatment, but the remaining 14 tested before treatment showed marked prolongation. During the treatment period the reconstitution time returned to normal in most cases, but in four (1 salicylate, 2 cortisone, and 1 A.C.T.H.) delayed reconstitution persisted in spite of clinical improvement, loss of symptoms, and a fall in temperature and sedimentation rate. Two to three weeks after cessation of treatment all cases returned to within normal range, except one adult on salicylate therapy, who discharged himself from hospital during treatment because he felt so well. He returned after a few days with a clinical relapse, and his reconstitution time had become prolonged once more. No striking difference was found between the effects on the reconstitution time of these three treatments.

Fig. 7 shows the effects of hormone therapy in three cases of Still's disease. All showed prolongation of reconstitution time before treatment and a fall towards normal during treatment. This fall was not so marked as in the rheumatic fever group, and all showed a return towards their previous abnormal level two to three weeks after cessation of therapy, except Case 1, a boy of 9, who made an apparently complete recovery from an acute first attack of Still's disease, with no residual arthritis. Case 3 had a relapse followed by a further prolongation of the reconstitution time.

Discussion

The findings described above and summarized in Table VI indicate that in the rheumatic diseases investigated (rheumatic fever and Still's disease) there is a delayed reconstitution time of the dermal barrier following the injection of hyaluronidase.* This is true only during the acute phase of rheumatic fever; with recovery from the acute attack a normal rate of reconstitution is resumed. It is possible, therefore, that delayed reconstitution of hyaluronic acid in the skin is a hitherto unrecognized aspect of the general connective-tissue disorder. In Still's disease the ability of the skin to reconstitute hyaluronic acid is impaired; 17 out of 18 cases described showed delayed reconstitution irrespective of their clinical activity. One case in which there was apparent complete recovery showed a return to normal (Case 1, Fig. 7). Of the rheumatic fever cases, three on hormone therapy, despite marked clinical improvement, remained at their previous abnormal level. Their reconstitution time, however, returned to normal in convalescence. It must be concluded that a return to normal reconstitution rate is a feature of recovery from acute rheumatic fever which is not influenced by cortisone or A.C.T.H.

In the three cases of Still's disease under hormone treatment the reconstitution time changed towards normal in parallel with the clinical improvement, but after treatment this change was maintained only in the case showing apparent complete recovery.

In the rheumatic group of diseases the mesenchymal connective tissue (synovial, myocardial, muscle and

TABLE VI.—*Summary of Results*

	Reconstitution Time in Hours							Total
	24	30	36	42	48	54	54+	
Normal children	6	5	1					12
Normal adults				13				13
Active R.F.					1	5	18	24
Conval. R.F.	4	5	7					16
Active Still's			1	1	2	4	5	13
Inactive Still's			1			1	3	5
Adult R.A.			1		2		1	4
T.B.	3	4	12					19

*A further 18 tests have given similar results (2 normal, 12 active, and 4 convalescent rheumatic fever cases).

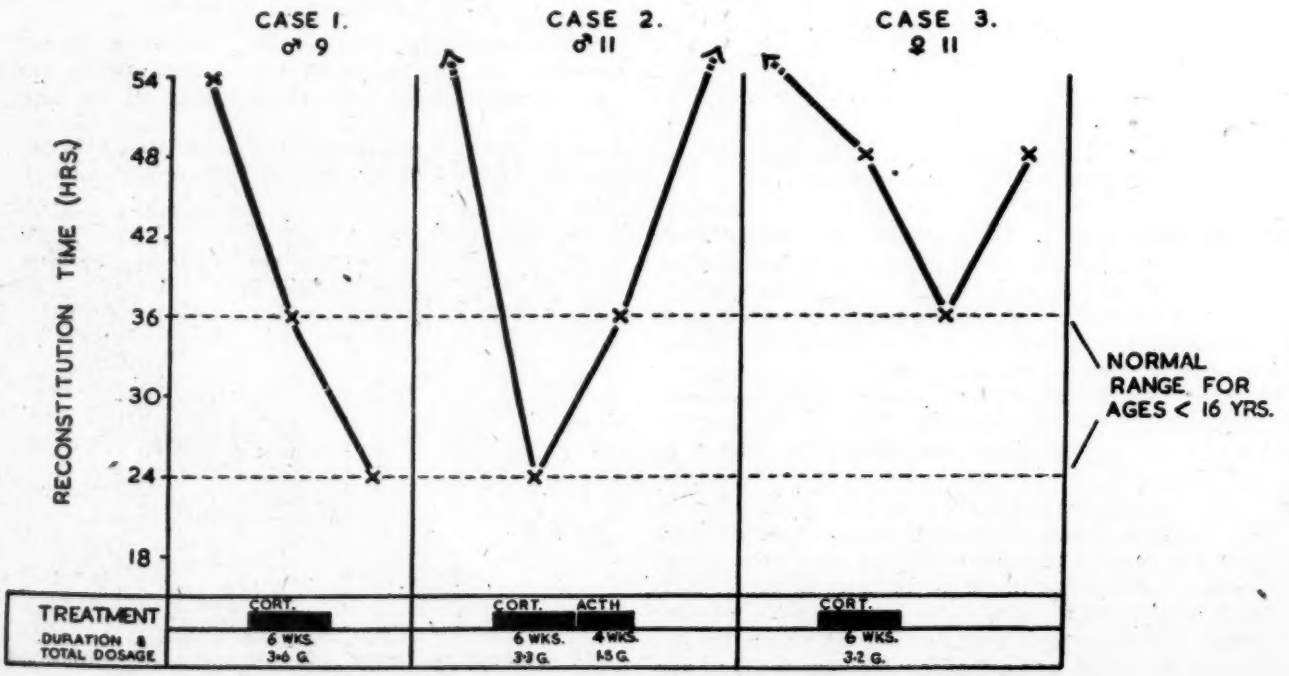

FIG. 7.—Effect of cortisone and A.C.T.H. on reconstitution times in Still's disease.

dermal connective tissue, joint capsules, bursae, and tendons) forms the target organ. This damaged tissue contains the major proportion of ground substance in the body, and the delayed reconstitution time which we have observed in the skin could be explained by a deficient synthesis of ground substance, due to altered cell nutrition or depressed cell activity.

The role of non-specific serum hyaluronidase inhibitor in the reconstitution of hyaluronic acid in the skin must also be considered. Dorfman (1950) showed this to be raised in acute rheumatic fever, but it was further shown (Dorfman and Moses, 1950) that the inhibitor was decreased by A.C.T.H. in this disease in parallel with clinical improvement. If this inhibitor (by direct action on the enzyme) affected the skin tests described here, a decrease in reconstitution time might be expected in the acute stages, and a prolongation during convalescence—the reverse of the changes actually found. This supports Hechter's (1947) conclusion that plasma anti-hyaluronidases do not significantly affect the spreading activity of the injected enzyme.

Summary

A method for measuring the "reconstitution of the dermal barrier" is described and errors in the technique are analysed.

The normal reconstitution time varies with age and lies between 24 and 42 hours.

We determined 214 reconstitution times—109 in rheumatic fever, 55 in rheumatoid arthritis, 27 in normal adults and children, and 23 in non-rheumatic controls. Reconstitution was prolonged in rheumatoid arthritis and in acute rheumatic fever, but returned to normal levels in the latter during treatment with salicylate, A.C.T.H., and cortisone, and during convalescence.

Non-rheumatic tuberculous controls with raised sedimentation rates gave normal readings.

It is concluded that in both rheumatoid arthritis and rheumatic fever there may well be an alteration in hyaluronic acid metabolism.

We would like to thank Dr. L. E. Glynn for encouragement and constructive criticism; Dr. Frank Fletcher, of Benger's Research Department, for turbidometric studies and a generous supply of hyalase; Dr. L. A. Key, of Heatherwood Orthopaedic Hospital, for permission to test a control series of patients; Dr. R. C. Hallam for assistance; normal volunteers for their co-operation; Mr. P. J. Fisk for the photographs; and the Central Syringe Service staff at this hospital, who rendered this investigation possible.

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An inquest at Dorchester on September 12 on a 64-year-old woman who died after a wasp sting revealed a most unusual hypersensitivity. Six years ago she was unconscious for some hours after a sting, and on September 10 she was again stung by a wasp. Immediately afterwards she was reported to feel shaky, perspiring, and trembling; she tried to vomit three times, complained of not being able to see, and died in about 15 minutes. At necropsy the heart was found to be contracted and virtually empty of blood, and apart from widespread atheroma no abnormalities were discovered. The cause of death was declared to be syncope.

THE EOSINOPENIC RESPONSE TO CORTISONE AND A.C.T.H. IN NORMAL SUBJECTS

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The eosinopenic response described by Hills, Forsham, and Finch (1948) has been widely used as an index of adrenocortical activity in man, particularly in studies of the response to A.C.T.H. (Forsham *et al.*, 1948), and as a test of adrenocortical function (Thorn *et al.*, 1948). It has also been used to assess the adrenocortical response to various forms of stress, such as surgery, the administration of adrenaline and insulin, and electric-convulsion therapy. The whole subject has been well reviewed by Prunty (1950) and by Sayers (1950), who both consider the eosinophil response in man to be a most useful index of adrenocortical function.

The eosinopenic response to cortisone mentioned by many workers reporting the effects of cortisone therapy has not been submitted to the same detailed study as the response to A.C.T.H., perhaps because much of the cortisone was given by injection and the slow response which follows this method of administration is not readily compared with the rapid response to A.C.T.H.; but Boland and Headley (1951) have noted that the clinical response to oral cortisone is both rapid and of short duration, the result of a single dose being similar to that of a single injection of A.C.T.H. On theoretical grounds the eosinopenic response to oral cortisone might be expected to give valuable information which would be complementary to that obtained from the response to A.C.T.H. We have therefore studied in some detail the eosinopenic response in normal subjects to both A.C.T.H. and oral cortisone in varying dosage.

Method

The number of circulating eosinophils was estimated by a modification of Dunger's (1910) method, using the following technique: blood is obtained from the thumb by a fresh needle prick and drawn up to the usual mark in a standard white-cell pipette. It is then diluted 1 in 10 by a freshly filtered solution of eosin 0.05% and acetone 5% in distilled water. After mixing well by shaking the pipette gently about 20 times, the usual first one-tenth is discarded and a double Fuchs–Rosenthal counting chamber is filled at once from the pipette. The chambers are left to stand for five minutes to allow the cells to settle and stain properly, after which all eosinophil cells in both chambers are counted with a ⅔-in. objective, using a bright light. To obtain the number of eosinophils per cubic millimetre of blood the number of cells counted is multiplied by a factor of 1.55. As in all blood-cell counting, the statistical error involved depends upon the number of cells counted, and the personal error can be minimized by much practice and careful standardization of technique.

The counts reported here were done by technicians who had been counting eosinophils regularly for periods

of a year or more. The accuracy of the sampling and counting technique was tested from time to time by doing duplicate counts and runs of duplicate sampling at frequent intervals. If two pairs of counting chambers are used for a single pipette the difference between the counts in each pair is in the region of ±5% for counts of 100 or over, though with very low counts the percentage error is of course considerably greater, and Table I

TABLE I.—*Consecutive Eosinophil Counts (Subject 1) During a Control Day and Between the Fourth and Sixth Hour after 50 mg. of Oral Cortisone. Two Pipettes were Filled from Each Needle Prick*

Time	Pipettes		Difference	Time	Pipettes		Difference
	1	2			1	2	
2·10	381	388	+7	1·50	56	34	−22
2·25	366	360	−6	2·5	50	38	−12
2·40	359	369	+10	2·20	59	44	−15
2·55	353	340	−13	2·35	56	41	−15
3·10	375	366	−9	2·50	62	47	−15
3·20	378	362	−16	3·0	69	62	−7
3·35	375	369	−6	3·10	72	59	−13
3·55	362	384	+22	3·20	78	62	−16
4·10	384	372	−12	3·35	84	78	−6
4·25	393	375	−18	3·45	99	72	−27

shows the type of result obtained over a two-hour period by filling two pipettes from one needle prick at intervals of 10 to 15 minutes during periods of average total counts and one of low total counts induced by cortisone. As might be expected, the second sample tends to give a slightly lower count than the first. Apart from this, both counts tend to fall and then rise again during the first experiment and to rise steadily during the second experiment, but there are no wild fluctuations between the consecutive counts or between the first and second pipettes. Since only fluctuations of over 50% in the number of circulating eosinophils are of any significance the technique is clearly adequate for our purposes.

In a monograph by Rud (1947), recently quoted in the *Lancet* (1950), it is claimed that the number of circulating eosinophils fluctuates wildly from one minute to the next, but Rud obtained his samples of blood from a cut in the ear which was reopened from time to time during the day, and indeed on successive days, and the eosinophils in the material obtained from this wound were estimated by counting a small sample and multiplying by a factor of 6.25. In view of the fact that the minute-to-minute differences of eosinophil count observed by Rud were of the same order as he observed at hourly or even daily intervals, it seems likely that many of these differences were due to his methods of sampling and counting, which are clearly open to grave criticism. At all events, we have not observed these rapid fluctuations of eosinophil count, though the count may rise and fall within a wide range over a period of hours, particularly under the influence of stress, cortisone, or A.C.T.H.

Plan of Study

Four male subjects aged 39, 43, 40, and 32 years were selected for the main investigations. They were all working in the department and carried on their usual routine, and except for subject 4, who was 6 ft. 5½ in. (197 cm.) in height, they were in no way remarkable.

Eosinophil counts were done between 9.30 and 10 a.m. on many days, and this is called the "morning" count. On two days each week, usually Monday and Friday, the eosinophils were counted at two-hourly intervals throughout the day. On different days single doses of cortisone or A.C.T.H. were given immediately after the morning count, and in addition a number of control days were interspersed throughout the investigation.

A.C.T.H. was given intramuscularly on the following dosage scale: 2.5, 5, 10, 20, 40, and, in two instances, 100 mg. Cortisone was given as a suspension by mouth on a dosage scale of 6.25, 12.5, 25, 50, and 100 mg. In a few experiments the same dosages of A.C.T.H. and cortisone were repeated, and in another series of experiments other preparations of A.C.T.H. and a number of peptide derivatives were also employed. The number of circulating eosinophils was also investigated during periods of stress produced by T.A.B. vaccine and by incidental disease.

Results

It is well known that the eosinophil count may be greatly influenced by intercurrent disease or unusual stress of any kind. Our studies have therefore been confined to "normal" days, unless otherwise stated, and Table II shows the distribution of "normal" morning

TABLE II.—*Distribution of Morning Eosinophil Counts in Four Subjects on "Normal" Days*

Eosinophils	Subjects			
	1	2	3	4
0–49				
50–99				
100–49				
150–99	1			4
200–49	2	1		6
250–99	10	3	9	9
300–49	5	3	11	2
350–99	7	5	9	2
400–49	1	5	4	
450–99	2	4		
500–49	3	2		
550–99	1	1		
600–49		3		
650–99				
Total counts ..	32	27	33	23

counts in the four subjects under investigation. In subject 1 the counts have a wide range from 150 to 599, centred around the 350 mark. In subject 2 the range is similar, from 200 to 649, but centred a little higher, about 400 or over. In subject 3 the range is small, all counts falling between 250 and 449; while in subject 4 there is again a small range from 150 to 399, centred around 250. Thus already in respect of their morning counts these four subjects differ considerably.

It has been customary to express short-term alterations in the eosinophil count as a percentage change, and we have followed this practice by expressing the counts throughout the day as a percentage increase or decrease over the morning count for that day.

During the control days the count increased, decreased, remained unaltered, or fluctuated slightly, the mean change throughout the day of all the counts on any one individual being no more than 10% of the morning count, so that there did not appear to be any consistent diurnal trend. Occasionally there was an increase or decrease of about 40%, and on one occasion an increase of 50%. The changes in the four and six-hour counts are summarized in Fig. 3, and it is clear that in our subjects fluctuations in the eosinophil count of up to 50% may be found during control days and must therefore be regarded as a normal occurrence.

After the administration of cortisone and A.C.T.H. a satisfactory decrease in the number of circulating

eosinophils was observed in subjects 1 and 2. For both substances the decrease began at two hours and was pronounced at four hours. With the higher dosages the count continued to decrease at six hours and was still low at eight hours, while with the lower dosages the count increased again at six hours and tended to return to or surpass the morning count by eight hours. Sample eosinophil depression curves from subject 1 are shown in Fig. 1, and it will be seen that the general shape of the cortisone and A.C.T.H. curves is remarkably similar.

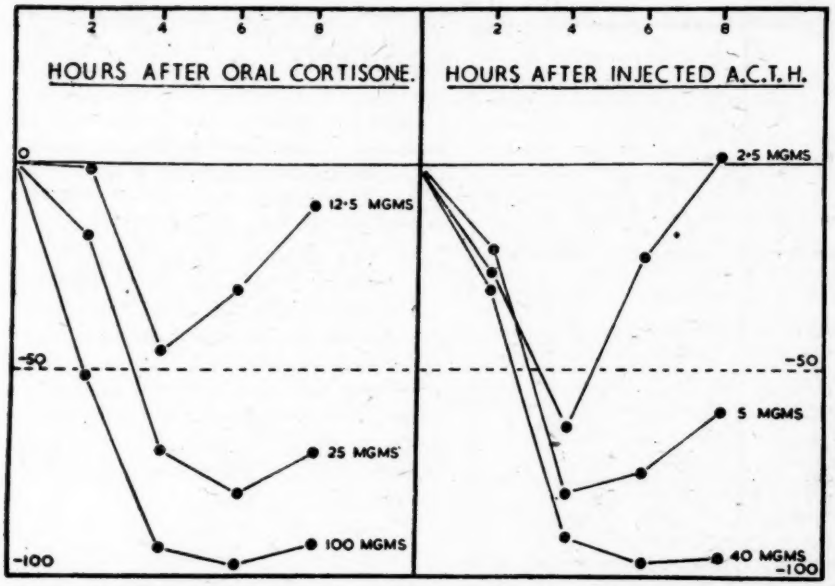

FIG. 1.—Shows percentile change in circulating eosinophils (subject 1) following single doses of oral cortisone and intramuscular A.C.T.H. at different dose levels.

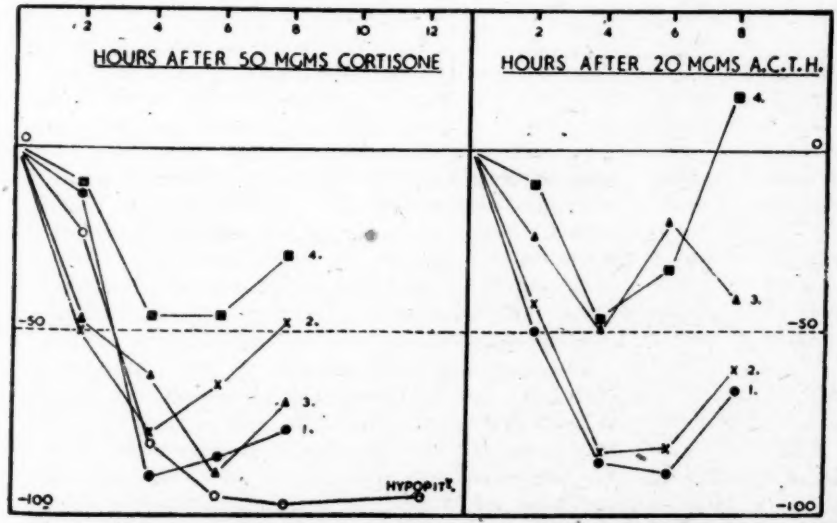

FIG. 2.—Shows percentile change in eosinophils in four subjects following single doses of 50 mg. of cortisone and 20 mg. of A.C.T.H. The clear circles show the effect of 50 mg. of cortisone in a case of severe hypopituitarism.

Fig. 2 shows the eosinophil depression curves produced by 50 mg. of cortisone and 20 mg. of A.C.T.H. in the four subjects under investigation. The responses to cortisone in subjects 1, 2, and 3 are not very dissimilar, but subject 4 fails to give a significant response. With A.C.T.H., subjects 1 and 2 give good depression curves, but subjects 3 and 4 fail to give significant responses.

From the shape of all the curves we have observed it is clear that nearly as much information can be obtained from the four- and six-hour counts as from the whole curve. We have therefore summarized our findings in respect of these counts in Fig. 3.

From this figure it will be seen that subject 1 responds well to both A.C.T.H. and cortisone in low dosage. Subject 2 also responds well to both hormones but at a slightly higher dosage. Subject 3 responds well to cortisone but fails to respond properly to A.C.T.H. even when 100 mg. was given as a single dose. Subject 4, on the other hand, fails to respond significantly to oral cortisone in doses up to 100 mg., but does respond to A.C.T.H. at the higher dose levels.

At first it was hoped that a study of eosinophil depression curves might provide a simple method for assaying the potency of different preparations of A.C.T.H., but repeated injection of the same dosage of the same preparations did not give strictly comparable curves. This is not surprising when we consider that the spontaneous fluctuations in the eosinophil count may occasionally be as great as 50% within the period of the test and that this might have to be either added to or subtracted from the fluctuation induced by the administered A.C.T.H. An accurate assay on these lines therefore seems to be out of the question, but a very rough guide to potency may nevertheless be obtained, particularly if the A.C.T.H. to be tested is given in two dose levels to subjects whose dose-response curves have already been constructed. Too great an accuracy must not, however, be aimed at.

If we consider a partial response to be a fall in the eosinophil count of over 50% at either four or six hours and a full response to be a fall of over 75% it is possible to construct a rough equivalent dosage table. This has been done in Table III for oral cortisone, the A.C.T.H. used in these studies, and two other A.C.T.H. preparations, one stated to be three times more potent than standard and a peptide derivative of this preparation said to be 5 to 15 times more potent than the original by rat assay. Though for assay purposes our results leave much to be desired, they do further illustrate the difference in responsiveness of our four subjects, and they might reasonably be used as a rough guide to the choice of preparation and the dosage likely to be required for therapy in the individuals concerned.

The most valuable result of these studies is, however, the demonstration of the differing responsiveness to cortisone and A.C.T.H. of our four male subjects, at least so far as their eosinopenic response is concerned.

In a previous experiment T.A.B. vaccine (10 ml. intravenously) was used to induce an acute febrile stress

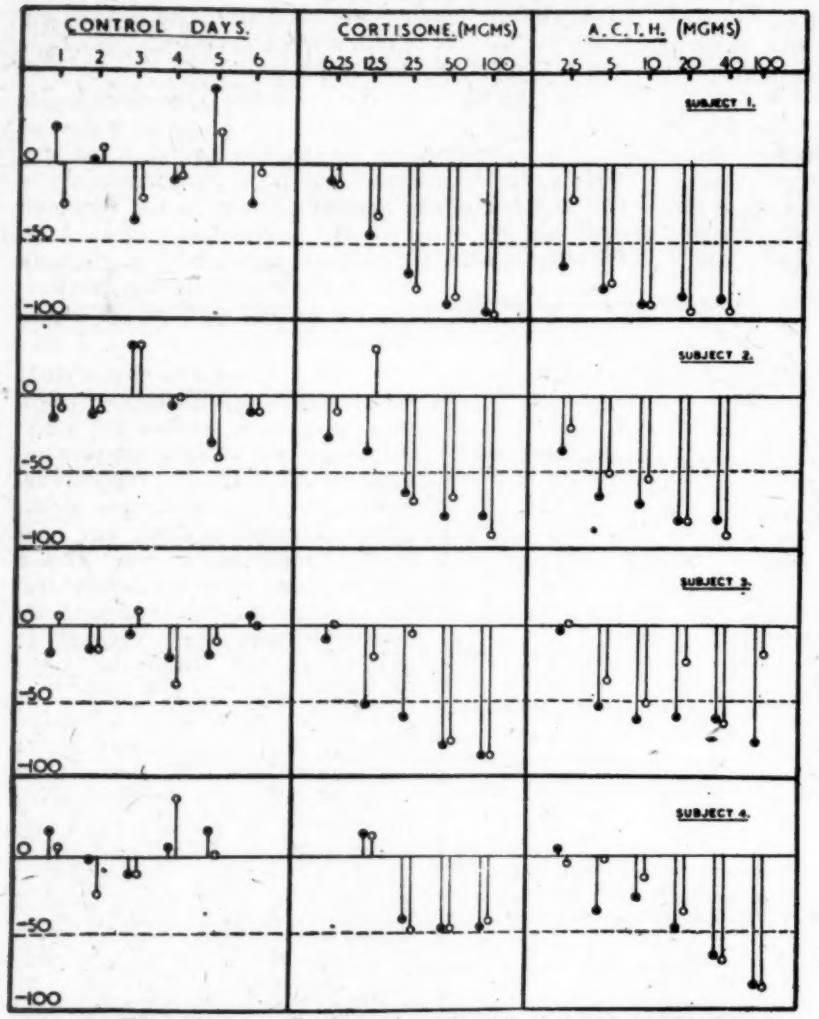

FIG. 3.—Shows the percentile change in eosinophils at four hours (black circles) and six hours (clear circles) in four normal subjects during control days and following varying doses of cortisone and A.C.T.H.

TABLE III.—*Approximate Dosage in mg. Required for Equivalent Response*

Subject	Response	Cortisone	A.C.T.H. J.24410	A.C.T.H. 84–85 H	A.C.T.H. Peptide	Stress
1	Partial	12·5+	2·5	2·5	?	
	Full	25	5	10	0·25	T.A.B. 10 ml. I.V.
2	Partial	25	5·10	?	0·25	
	Full	50	20	2·5	1·0	
3	Partial	25	5–100	2·5–20	2·0	T.A.B. 10 ml. I.V.
	Full	50	?	?	?	Septicaemia
4	Partial	100+	40	2·5	1·0+	
	Full	?	100	10	?	

TABLE IV.—*Comparison of Eosinopenic Response to 25 mg. A.C.T.H. and Febrile Stress Produced by T.A.B. in Four Normal Subjects and Two Patients with Rheumatoid Arthritis*

Subject	No.	A.C.T.H. 25 mg.		T.A.B. 10 ml. I.V.	
		Eosinophil Change	% Fall	Eosinophil Change	% Fall
Normal subjects ..	1	278–7	97	284–15	95
	6	362–7	98	405–23	95
	5	400–144	64	293–96	66
	3	318–137	57	354–118	66
Patients ..	1	59–22	62	59–23	60
	2	200–25	87	225–50	78

in two patients with rheumatoid arthritis and four normal subjects, including subjects 1 and 3 of the present investigation. The resultant eosinopenia was compared with that produced by a single dose of 25 mg. of A.C.T.H. of a different preparation from that used in the rest of this study. The results summarized in Table IV show that for each individual the degree of the eosinopenic response was about equivalent, although it was of longer duration with T.A.B. than with A.C.T.H. In this experiment also the relative unresponsiveness of subject 3 compared with subject 1 is evident. On the other hand, subject 3 is capable of producing a complete eosinopenic response, as his count fell to zero during the onset of a steptococcal septicaemia (Table III).

It was thought that the differing responsiveness of our four subjects might be reflected in differing urinary excretions of formaldehydogenic steroids; but estimations of these steroids by Bassil and Hain's (1950) method in three 24-hour specimens for each of our subjects during control days gave similar results, all of which were within the normal range.

Discussion

Our findings show that even among normal subjects there may be marked differences in the eosinopenic response to single doses of cortisone and A.C.T.H.

It is interesting to note that subjects 1 and 2, who gave satisfactory eosinopenic responses to small doses of both hormones, also showed a wide range of fluctuation in their morning counts, while subjects 3 and 4, who were less responsive to the hormones, also showed less variation in their morning counts. Furthermore, in the six subjects in whom the eosinopenic responses to T.A.B. and A.C.T.H. were compared there appeared to be some correlation between the degree of this response to both stress and injected A.C.T.H. in each individual.

The fact that responsiveness to A.C.T.H. and oral cortisone may be dissociated as in subjects 3 and 4 suggests that the eosinophils themselves cannot be wholly responsible for the difference of responsiveness between one individual and another. A poor response to oral cortisone might result from failure of absorption or destruction of the hormone in the gut, and failure of response to injected A.C.T.H. might result from the development of anti-hormone or the destruction of the A.C.T.H. by tissue enzymes, so that there are clearly many factors to be considered. Nevertheless, the response to A.C.T.H. has been shown to provide useful information in endocrine disorders (Thorn *et al.*, 1948; Prunty, 1950), and in three cases of established panhypopituitarism we have noted a greatly exaggerated and prolonged eosinopenic response to oral cortisone, one example of which is shown in Fig. 2. But to what extent these eosinopenic responses can be more generally applied to assess the state of activity of an individual's

pituitary adrenal mechanism is still a matter for speculation.

At this stage, however, it is sufficient to note that the eosinopenic response to A.C.T.H. and oral cortisone in normal subjects can be usefully compared, and it remains to be seen whether the application of a combined A.C.T.H.–cortisone response test to patients with rheumatic, endocrine, and other diseases will give information of practical value.

Summary

A convenient modification of Dunger's technique for estimating the number of circulating eosinophils has been described and shown to be accurate enough for experimental purposes. By the use of this technique the eosinopenic responses to single doses of oral cortisone and intramuscular A.C.T.H. have been studied in some detail in four normal subjects. It has been shown that the time relations of the responses to these two hormones are remarkably similar, but that there may be considerable individual variations in responsiveness to either cortisone or A.C.T.H., or both.

The eosinopenic response to various A.C.T.H. preparations and to stress have also been compared, and throughout these studies the differences of individual responsiveness of our subjects have been maintained. Three patients with panhypopituitarism showed an eosinopenic response to oral cortisone which was exaggerated and prolonged. In spite of the many factors which may influence eosinopenic responsiveness it is suggested that a study of the eosinopenic response to 50 mg. of oral cortisone, added to the already well-established A.C.T.H. response test, might provide a useful guide to therapy with these hormones in the individual concerned, and might possibly give some indication of the state of activity of the individual's own pituitary–adrenal mechanism.

The cortisone used in this work was provided from a generous gift made jointly to the Nuffield Foundation and the Medical Research Council by Merck and Co., Inc. We are indebted to the Medical Research Council and Organon Laboratories for the A.C.T.H. used; to Dr. Kenner, of the Chemical Laboratories of Cambridge University, for the peptide fraction; and to Mr. D. S. Jackson for the steroid assays.

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Speaking at a meeting of the Society of Public Analysts recently about the chemical quality of milk Dr. J. G. Davis said that it was frequently stated that the overall composition of milk in this country had deteriorated during the last few years. It was difficult, if not impossible, to prove this contention by adequate scientific evidence for the whole country, and the reasons for this were discussed. A review of existing information was given, and data received from a number of public analysts on the composition of milk as sold over the period 1900–51 were presented. Not all records showed a fall in composition over a long period, and yearly and regional variations may be of the same order as the fall which it was claimed has taken place.

EOSINOPHIL COUNTING: A MODIFICATION OF PILOT'S METHOD

BY

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The use of A.C.T.H. and cortisone entails the quantitative determination of the circulating eosinophils at frequent intervals as one of the pathological tests employed as a potential measure of the efficacy of the drugs. The method most commonly in use is that originally described by Randolph (1944). The object of this paper is to call attention to the diluting fluid evolved by Pilot (1950) and to the modification of that fluid it has been necessary to make in this laboratory.

Pilot investigated the counting fluids that had already been described. From them he selected as the best those of Randolph (1944) and Rud (1947), and combined the better properties of each in his diluent. Randolph's fluid, a phloxine–methylene-blue stain in propylene glycol, has certain advantages. The glycol base renders the red blood cells relatively non-refractile, and acts as a vehicle for both acid and basic stains, while, being viscous, it does not evaporate quickly. There is no deterioration of the count obtained when the fluid and blood are left in the pipette overnight. All the leucocytes, however, are stained, and a high-power objective is necessary for differentiation of the eosinophils. The methylene blue and phloxine components of the stain must be kept separate until just before use, for after they have been mixed for four hours precipitation of the dyes occurs and with it a loss of differential staining detail. The Rud fluid, a magdala-red stain in acetone, likewise has an advantage. By the use of a small amount of sodium carbonate (0.1%) all leucocytes other than the base-resistant eosinophils are lysed. Its disadvantage is the use of acetone as the vehicle. As this substance is highly volatile, the chambers must be flooded at once on shaking and kept in a moist Petri dish for 15 minutes before making the count.

Pilot decided to use the concentration of base employed by Rud in the propylene glycol vehicle of Randolph. Since the leucocytes other than the eosinophils were lysed, only a single stain was necessary, and no differential count was involved. As stains he used phloxine (0.1%), eosin (0.05%), and magdala red (0.05%), all with equally good results. His diluting fluid he compared with those of Randolph (1944), Rud (1947), and Dunger (1910), employing double counts in a series of 1,000 observations on human blood, with results more nearly constant than those obtained with the other fluids.

The stain he suggested is obtained by mixing the following ingredients: 50 ml. propylene glycol, 40 ml. distilled water, 10 ml. 1% phloxine in water, and 1 ml. 10% sodium carbonate in water. It is necessary to wait for 15 minutes after collection of the count to allow for proper lysis and staining, these occurring in either pipette or chamber.

Investigation

We have investigated Pilot's fluid in this laboratory for a period of four months, and the results obtained by its use are comparable to those obtained by the use of Randolph's fluid. The fluid possesses all the qualities claimed by Pilot. The use of a low-power objective is adequate, for the eosinophils alone are stained and visible, and the counting is thereby both easy and rapid. Pilot claims that there is no perceptible drop in counts done within three hours of collection and that there is an average drop of 35% in the count when the pipette lies for 24 hours. It has been found here that the timing is much more critical than he suggests. The accompanying table shows the results of standing the pipettes for four hours, and a considerable variation in the counts has been noticed after a stand of only one hour. The table shows the results obtained in 10 unselected cases taken from the total of 36 cases so investigated.

When the delay between collection of the blood and counting was less than one hour it was found that the eosinophils were spread homogeneously throughout the chambers, and the totals in each approximated closely. When, however, the delay exceeded one hour the scatter of cells was not even, and fallacies resulted. To investigate the error entailed by a delay in counting, a period of four hours was selected as being the maximum period likely to elapse between collection and counting in a laboratory where routine haematology was more imperative and yet where the eosinophil counts had to be collected four hours after the morning injection of either A.C.T.H. or cortisone. The error is shown in the table. Counts were done from duplicate samples of blood immediately after collection and after a delay of four hours.

Table Showing the Effects on Eosinophil Counts of Standing Four Hours, Using Pilot's Fluid, With and Without the Use of Heparin

Case No.	Procedure	3rd Drop from Pipette					7th Drop from Pipette					12th Drop from Pipette					Mean Chamber Count	Eosinophil Count per c.mm.
		Chamber Counted				Total	Chamber Counted				Total	Chamber Counted				Total		
		1	2	3	4		1	2	3	4		1	2	3	4			
1	Immediate counting	14	13	12	13	52	13	12	11	13	49	13	13	12	12	50	12·6	140
	Stood 4 hours unmodified	8	**10**	**7**	**8**	33	10	**5**	**6**	**5**	26	4	**5**	4	**8**	21	6·7	74
	Stood 4 hours heparinized	12	11	15	13	51	10	14	11	13	48	12	10	12	14	48	12·3	137
2	Immediate counting	32	34	31	32	129	31	30	30	32	123	30	29	32	30	121	31·1	345
	Stood 4 hours unmodified	**27**	**18**	**37**	**30**	112	**19**	**27**	28	**19**	93	**28**	**25**	**48**	18	119	27·0	300
	Stood 4 hours heparinized	33	34	28	31	126	32	38	35	29	134	32	29	31	29	121	31·8	353
3	Immediate counting	30	32	32	30	124	29	30	31	32	122	30	33	32	30	125	30·9	343
	Stood 4 hours unmodified	17	**14**	**20**	19	70	**11**	**19**	16	**13**	59	22	**16**	**27**	**26**	91	18·3	203
	Stood 4 hours heparinized	33	31	29	31	124	30	35	30	31	126	28	33	30	32	123	31·1	345
4	Immediate counting	28	31	29	30	118	28	29	31	33	121	28	28	26	31	113	29·5	327
	Stood 4 hours unmodified	**35**	**33**	**50**	**29**	147	**23**	**14**	**53**	**25**	115	**19**	24	**41**	**21**	105	30·6	340
	Stood 4 hours heparinized	32	28	29	34	123	29	30	33	28	120	30	32	27	29	118	30·3	336
5	Immediate counting	10	9	9	10	38	8	9	11	13	41	9	8	13	11	41	10·0	111
	Stood 4 hours unmodified	4	3	**38**	5	50	**5**	3	5	**3**	16	2	8	5	4	19	7·1	79
	Stood 4 hours heparinized	11	9	10	9	39	10	10	10	13	43	9	10	9	9	37	10·0	111
6	Immediate counting	48	53	47	50	198	52	48	51	51	202	47	49	56	57	209	50·8	564
	Stood 4 hours unmodified	**41**	28	**31**	**34**	134	36	33	**56**	39	164	31	**54**	29	**41**	155	37·8	420
	Stood 4 hours heparinized	51	49	55	56	211	50	54	47	53	204	51	55	53	46	205	51·7	574
7	Immediate counting	24	20	21	27	92	24	23	27	26	100	23	25	24	20	92	23·7	263
	Stood 4 hours unmodified	**2**	4	**4**	**4**	14	**4**	5	4	**3**	16	**2**	**5**	6	10	23	4·4	49
	Stood 4 hours heparinized	20	24	26	28	98	26	25	22	26	99	25	23	24	22	94	24·3	270
8	Immediate counting	2	2	3	3	10	2	4	3	2	11	3	2	2	4	11	2·6	29
	Stood 4 hours unmodified	0	0	2	2	4	**4**	**6**	**0**	2	12	**3**	0	**0**	1	4	1·7	19
	Stood 4 hours heparinized	2	3	3	**3**	11	3	3	4	4	14	3	2	3	2	10	2·9	32
9	Immediate counting	25	27	25	29	106	27	29	30	25	111	24	27	26	24	101	26·5	294
	Stood 4 hours unmodified	**12**	13	**20**	21	66	**15**	**24**	14	15	68	**20**	16	**20**	24	80	18·8	209
	Stood 4 hours heparinized	27	26	28	25	106	26	24	27	28	105	29	26	27	25	107	26·5	294
10	Immediate counting	12	14	14	13	53	16	12	14	14	56	14	12	16	15	57	13·8	154
	Stood 4 hours unmodified	**6**	**8**	10	**7**	31	**7**	**12**	6	8	31	9	**8**	**8**	10	35	8·0	89
	Stood 4 hours heparinized	13	14	12	13	52	13	17	12	12	54	12	14	13	12	51	13·1	145

The figures in black indicate that clumps of cells were visible in the counting chamber.

The routine procedure followed has been to collect blood from a fingerprick in the proportions indicated by Pilot (blood to the 1 mark in a white-cell diluting pipette, diluted to the 11 mark with fluid), the blood and diluting fluid being mixed thoroughly by rotation during and after collection. Before counting, the pipette has been shaken for two minutes in a mechanical shaker of the type described by Sanders *et al.* (1950). Four chambers of a Neubauer haemocytometer were flooded, and counts made of the eosinophils contained in all nine squares of each. The number of eosinophils contained in a cubic millimetre is calculated by multiplying the average number of cells per chamber by 11.1. It is clear from the table that appreciably more accurate results are not obtained by counting eight or more chambers rather than four.

The possible cause of this error was obvious microscopically. When the pipette had stood for four hours, or in the majority of cases for only one to two hours, small aggregations of cells were visible in almost every chamber examined. These clumps appeared to be composed of ghost leucocytes apparently bound together by a finely meshed stroma, and they contained varying numbers of eosinophils. The count obtained from such chambers depended upon whether or not a relatively large clump containing many eosinophils lay within the counting area of the chamber. If it did, the count was raised above that obtained from the immediately counted preparation: if it did not, the count might be greatly lowered.

That the deviation of the results was due to insufficient mixing of the blood and diluting fluid was eliminated by counting four chambers from the third drop from the shaken pipette, four from the seventh drop, and four from the twelfth drop, these being roughly the specimens

obtained from the bottom, middle, and top of the bulb. The table shows the scatter of cells to have been even throughout the pipette in every case, both in chambers flooded from pipettes immediately examined and in those which had been allowed to stand for four hours.

That these clumps of cells could not be broken up by prolonged shaking was proved in four cases by shaking a duplicate pipette for ten minutes, the microscopical appearances remaining unchanged. The homogenicity of the counts obtained from 12 chambers flooded within 30 minutes of collection and the absence of clumping in all counts thus examined gave sufficient proof that clumping was not due to insufficient mixing of blood and diluting fluid at collection. To check this, four duplicate pipettes were shaken for two minutes immediately after collection and again after standing for four hours. Clumps still appeared in the majority of chambers examined.

In an attempt to prevent this error, due possibly to the normal clotting of the blood within the pipette, heparin was added to the diluting fluid in a concentration of one unit per millilitre. The table shows that this addition completely eliminated the error, the counts so obtained on blood which had stood for four hours being closely comparable to those obtained on immediate counting. Nor were clumps visible microscopically in the preparations.

Such clumping does not follow the standing of pipettes when Randolph's fluid is used. Though the addition of heparin eliminates the error when using Pilot's fluid, it is unlikely, therefore, that a clotting mechanism alone is responsible. The answer possibly exists in the *p*H difference between the two stains. The *p*H of Randolph's fluid is 7.4, that of Pilot's fluid 10.55. The alkaline *p*H of the latter would allow of possible partial denaturing of the blood proteins, fibrin being the first partially to precipitate with *p*H variation. The use of buffer solutions other than sodium carbonate to produce a *p*H of 10.55 brought about similar clumping of the cells on standing.

Two further crude tests have been employed to establish that the stroma which binds the cells on standing is fibrin. First, streptokinase (Cathie, 1949) has been added to the diluting fluid in a concentration of approximately four units per millilitre. This experiment has been done in six duplicate tests. The counts obtained after a delay of four hours when using such a modified stain are, within experimental error, those obtained following the use of heparin and those resulting on immediate counting of unmodified fluid preparations. Secondly, 1 ml. of blood has been added to 9 ml. of diluting fluid and the mixture allowed to stand for four hours. Flooded over a white surface, the fluid shows macroscopic clots which, when gathered from several specimens and sectioned, appear to consist of a stroma of material staining as fibrin enmeshing eosinophils and other leucocytes. A more detailed investigation of this problem is proceeding.

Summary

Attention is drawn to Pilot's fluid for the enumeration of eosinophils. Counting is much easier and quicker than with Randolph's fluid, while the disadvantage of Rud's fluid is also overcome.

A source of error in the use of the fluid is the clumping of leucocytes on standing. This may be eliminated by the addition of heparin to the fluid in the concentration of one unit per millilitre. There is some evidence that this clumping is due to the formation of fibrin within the pipette.

We are indebted to Dr. I. A. B. Cathie, clinical pathologist, in whose laboratory the investigation was carried out, for much helpful advice and criticism.

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ADDISON'S DISEASE WITH ASSOCIATED POLYARTHRITIS

AN AETIOLOGICAL STUDY OF THE ARTHRITIS SYNDROME

BY

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In view of the therapeutic response to cortisone (compound E) in Addison's disease and in rheumatic diseases some correlation between these two disorders might be expected. In the literature, however, the association of the two diseases is notably infrequent. Bauer *et al.* (1951) could find no record of active rheumatoid arthritis in association with untreated Addison's disease.

Addison's disease is undoubtedly an endocrine disorder, but the possibility that the rheumatic diseases are fundamentally due to an endocrine disorder has not been demonstrable by clinical, laboratory, or pathological investigation. Some authors (Dejean, 1947; de Gennes *et al.*, 1947; Laroche, 1947a, 1947b) have reported Addison's disease with rheumatic joint lesions in cases under treatment with deoxycortone acetate (D.C.A.).

Selye (1949) noted that rats treated with large doses of D.C.A. often developed joint lesions which had histological changes characteristic of rheumatic arthritis and periarthritis. These lesions occurred in only a percentage of the rats, although some rheumatic manifestations were present in all. In some rats in which the arthritis appeared within a few weeks it was noted that the arthritic lesions cleared in spite of continued administration of D.C.A. Rarely, the arthritic lesions progressed to lesions comparable to those seen in rheumatoid arthritis. Selye found that if rats were adrenalectomized before the administration of D.C.A. they were more susceptible to these toxic effects of D.C.A. on the joints. He observed that cortisone relieved the arthritis. He stated that the significant aetiological factor in the genesis of the rheumatic joint lesions is an imbalance between the mineralo-corticoids of the adrenal cortex and the gluco-corticoids.

The following case is presented on account of the current interest in the aetiology of arthritic lesions.

Case Report

A farmer aged 58 had had for 15 years recurrent attacks of polyarthritis affecting his fingers, carpus, wrists, elbows, shoulders, and occasionally his knees. In 1939 he developed lobar pneumonia and empyema, which necessitated a thoracotomy and drainage. A chronic discharging sinus resulted, and this persisted for 10 years. In 1949 Mr. Stanley Wilson performed a lobectomy, and the sinus was successfully closed. In 1949 he developed an attack of polyarthritis affecting the fingers and wrists and other joints to a less extent. Dr. Raymond Kirk diagnosed rheumatoid arthritis. After a short course of gold therapy the arthritic changes subsided.

In April, 1950, he developed pain and swelling in his left hip, and a fluctuant swelling, from which pus was aspirated, developed over the great trochanter. A positive guinea-pig test proved this to be tuberculous. About this time he became excessively weak, his appetite failed, and he lost weight steadily. He developed a notable craving for salt, and at intervals was nauseated and had bouts of vomiting. Addison's disease was diagnosed in February, 1951, and treatment with 10 mg. of D.C.A. intramuscularly and 6 g. of sodium chloride daily was started 10 days before admission to hospital.

On admission to Dunedin Hospital on March 7 he was wasted and weak. His head hair was soft and fine and his body hair was scanty. Axillary and pubic hair was of normal distribution but somewhat scanty. There was generalized increase of pigmentation, most pronounced at the pressure areas and in the skin creases. The nipples and scrotum showed marked pigmentation. A few patches of pigmentation were present in the mucous membranes of the mouth. On the arms there were some small pin-point areas where pigmentation had been lost. The respiratory system was normal. The apex beat was in the fifth left interspace 4¼ in. (12.1 cm.) from the midline. The sounds were regular and of moderate intensity; the rate was 100. There was a presystolic gallop rhythm. The blood pressure was 118/64. The joints were normal.

Investigations.—The urine was normal. Radiography showed the chest to be clear, and a plain radiograph of the abdomen showed no adrenal calcification. Gastric analysis revealed a hypochlorhydria. Blood count: red cells, 3,430,000; haemoglobin, 64%; white cells, 5,900 (11% eosinophils). The serum sodium was 288 mg. per 100 ml. and the serum potassium 19 mg. per 100 ml. The Congo red test for amyloid disease was normal.

Treatment

At the time of admission no cortisone was available and treatment was continued with 10 mg. of D.C.A. and 6 g. of salt daily. Five days after admission he developed arthritic changes of the carpo-metacarpal joint of the forefinger on the left hand and the left elbow. The joints were swollen and tender, and movement was restricted by pain. The following day diarrhoea began and his fluid output fell to 240 ml. There was a deterioration in his general condition. The blood pressure fell to 100/68. The heart was fibrillating. (E.C.G. report: There is an irregular rhythm, possibly auricular fibrillation. There is a suggestion in Lead V_2 of a nodal type of rhythm. The rate is 70 a minute. Standard leads show low-voltage T waves throughout. Chest leads: there is counter-clockwise rotation, transition point being between V_1 and V_2. The T wave is flattened but upright. It is of very low voltage in V_5. The shape of the QRS is not abnormal. The Q–T time looks prolonged. Unipolar limb leads show that the heart tends to be horizontal. There is a low voltage throughout. T waves are indeterminate.) In the next three days there was further deterioration. The urinary output fell to 100 ml. and the blood pressure could not be recorded. The patient became confused, disorientated, and incontinent, and was in a state of toxic delirium. The 17-ketosteroids were 1.3 mg., the serum sodium was 288 mg. per 100 ml., and the serum potassium rose to 24 mg. per 100 ml. The serum uric acid was 2.8 mg. per 100 ml.

Treatment with cortisone (Merck) was begun on March 18, with 300 mg. intramuscularly followed by 100 mg. daily. The D.C.A. was increased to 20 mg. daily and the salt maintained at 6 g. daily. He was given digitalis from the onset of fibrillation.

Thirty-six hours after cortisone was begun there was a striking improvement in his general condition. The toxic delirium cleared; he became continent and the urinary output rose; and his heart sounds improved. He improved for the next 19 days while cortisone treatment was maintained—100 mg. for eight days and 50 mg. thereafter. After 10 days the D.C.A. was decreased to 10 mg. daily.

Five days after the onset of treatment with cortisone the joint swellings had subsided completely. The eosinophil count fell to zero. Screening at the conclusion of cortisone therapy showed a considerable increase in the size of the heart. The electrocardiogram showed left ventricular preponderance. The serum sodium rose to 306 mg. per 100 ml., the uric acid was 2.7 mg. per 100 ml., and serum potassium fell to 18 mg. per 100 ml.

When supplies of cortisone failed, D.C.A. by injection was discontinued and 100 mg. was implanted into the abdominal wall. This small dose was chosen on account of observed cardiac enlargement. The salt was reduced to 1 g. daily. A week later the patient began to show signs of further deterioration. The blood pressure fell, the pulse increased, and he complained of swelling, pain, and tenderness of the second left metacarpo-phalangeal joint and the left medio-carpal joint.

Cortisone became available again, and 100 mg. was injected daily. Two days later there was an improvement in his general condition and the arthritic changes subsided.

A further trial was carried out: cortisone was discontinued and D.C.A. was recommenced (10 mg. daily), and salt was increased to 8 g. daily. Three days later he complained of pain in his right shoulder. On examination the joint appeared normal. The following day the right elbow became swollen, tender, and reddened, and in the next two days the right medio-carpal joint and both elbow-joints became swollen, hot, and tender. A day later the small joints of the right middle finger swelled and most of the finger-joints of the left hand were involved. On the same day there was a general deterioration with a fall in blood pressure and tachycardia, and the serum sodium fell to 260 mg. per 100 ml.

Cortisone was recommenced—300 mg. daily for two days, and then 100 mg. daily. Within three days all arthritic changes had subsided and full range of movement was restored in the affected joints. He was transferred to a convalescent hospital for three weeks on a maintenance dose of cortisone, 50 mg. daily, and salt, 4 g. daily. The improvement was maintained and his weight increased by 11 lb. (5 kg.) in three weeks.

A week later cortisone and salt were discontinued again, and D.C.A. 10 mg., and promethazine hydrochloride ("phenergan") 1 mg., an antihistaminic, were given daily. Within five days the arthritic lesions recurred and were again controlled when cortisone, 100 mg. daily, was given.

Discussion

This patient presented a picture of Addison's disease with associated polyarthritis. After the diagnosis of Addison's disease, salt and D.C.A. therapy was begun, and soon after admission to hospital six weeks later there was painful arthritis involving the carpus joints of both hands. When cortisone was added to the therapeutic regime the arthritis promptly settled. When cortisone supplies failed and salt and D.C.A. were increased, arthritis returned in a more severe form, affecting interphalangeal joints of the hands, the carpus joints, and both elbow-joints. Again on resuming treatment with cortisone the arthritic lesion cleared promptly within four or five days.

Selye (1949) reported a technique for the production of an acute arthritis and periarthritis by the injection of formaldehyde into the vicinity of joints. If large doses of formaldehyde were administered the acute stage was followed by a very prolonged chronic arthritis and periarthritis characterized by moderate oedema and pronounced connective-tissue proliferation. This chronic arthritic condition continued to proliferate for weeks after the initial injection of irritant. He also found that this arthritis was aggravated by a preliminary treatment with D.C.A. or crude anterior pituitary extract, and it could be almost completely inhibited by cortisone or adrenocorticotrophic hormone (A.C.T.H.), suggesting an antagonistic relationship between D.C.A. and crude anterior pituitary preparations on the one hand and cortisone and A.C.T.H. on the other hand.

In a recent paper Selye (1951) further reports that with electrophoretically pure somatotrophic hormone (S.T.H.) (growth hormone) he can increase the sensitivity of the rat to the production of experimental arthritis. He concludes that the S.T.H. appears to play a part equally as important as A.C.T.H. The former is responsible for the activity of the mineralo-corticoids which produce arthritic changes, whereas the latter regulates the secretion of the gluco-corticoids which protect against the formation of arthritis.

In discussing Selye's findings the *British Medical Journal* (1951) suggested that the effects obtained may be those of a non-specific allergic reaction to foreign substances. Selye (1950) has shown that naturally occurring desoxocortisone (Reichstein's compound "S") also causes the lesions, making this explanation very unlikely; and he finds the suggestion of allergy difficult to reconcile with the fact that among a group of adrenal steroids tested only those with mineralo-corticoid activity exert such an allergic action, while among a group of proteins tested only pituitary extracts with somatotrophic hormone activity elicit comparable changes under experimental conditions.

Furthermore, if considerations are limited to cattle pituitary proteins it is found that A.C.T.H. inhibits while S.T.H. enhances the development of these collagen lesions. Adrenalectomy prevents this detrimental effect of S.T.H.-containing pituitary extracts. This also argues against their allergic nature, since adrenalectomy generally sensitizes the rat to allergic responses. It is also known that salt supplements the unilateral nephrectomy in sensitizing the organism to the actions of the mineralo-corticoids and of S.T.H.-containing pituitary extracts. Neither of these factors influences the course of allergic reactions. In our patient it was notable that the administration of an antihistaminic (promethazine hydrochloride) with D.C.A. failed to prevent the development of the polyarthritis in the absence of cortisone. Also it seems unlikely that D.C.A., which is so closely allied to a naturally occurring substance that is not a protein, should act in this manner. Furthermore, if this response of the joints to D.C.A. and salt was an allergic reaction, it would be reasonable to expect it to occur promptly within 24 hours or less, whereas it has appeared three to five days after the D.C.A. and salt had been given.

Just as a rat treated with formaldehyde in the vicinity of a joint is predisposed to develop arthritis, it is apparent, from the long history of recurrent rheumatic joint lesions, that our patient was predisposed to develop arthritic lesions. The salt and D.C.A. acted as an aggravating factor and precipitated an attack of rheumatic joint disease. It has been stressed that the clinical association of Addison's disease and rheumatic joint lesions is notably infrequent, and this in spite of the free administration of D.C.A. and salt to many patients with Addison's disease.

On this account we cannot subscribe in detail to Selye's contention, but suggest that, provided there is a pre-existing tendency in an individual to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of these lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids of the adrenals.

Summary

A case of Addison's disease and recurrent polyarthritis is described.

Treatment with D.C.A. and salt appeared to precipitate an attack of polyarthritis with swelling and pain. Cortisone readily controlled this arthritis.

Also, an antihistaminic given with D.C.A. failed to protect the patient from the polyarthritis, which was again controlled with cortisone.

The pathogenesis of rheumatic joint lesions is discussed. It is concluded that, if there is a pre-existing tendency to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of the joint lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids.

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PENICILLIN TREATMENT OF ACUTE MASTOIDITIS IN CHILDREN

BY

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In July, 1949, I presented to the International Congress of Otolaryngology a report on 50 cases of acute mastoiditis in children treated with penicillin injections between July, 1946, and July, 1948. So far as is possible these cases have been followed up, and it would now seem appropriate to discuss them, note what was attempted, and assess progress up to the time of writing.

Diagnosis

In 1946 it was decided to attempt the treatment of obvious acute mastoiditis or abscess by penicillin injection alone. The selected cases were to be those admitted to hospital as emergencies under the diagnosis of acute mastoid abscess, because during the course of an acute suppurative otitis media a post-aural inflammatory swelling had appeared. It was most important that all cases should be true acute conditions and not post-aural abscess consequent upon exacerbation of chronic tympano-mastoiditis.

Dependence was placed for this upon careful history taken from a parent or other responsible source. All 50 cases eventually collected appeared as the typical post-aural inflammatory swelling accepted as mastoiditis or mastoid abscess, and in 25 of them fluctuation was detectable on first examination or became evident later under treatment as the surrounding swelling settled.

The general condition of the children varied from normal to high fever. As a rule there was little pain, this having eased as the swelling appeared behind the ear. All cases had active otitis media, with otorrhoea present in 31 and absent in 19 at the time of the first examination. The duration of this otitis media, judged so far as was possible by the onset of pain, varied from one day to two months. Most cases had had some treatment, often by sulphonamides, previous to being admitted to hospital, but this was ignored.

These cases were considered suitable for a clinical trial of penicillin injections because they presented a good clinical picture easy for day-to-day assessment. They were not, as commonly thought, surgical emergencies, but could quite safely be kept under trial treatment for a few days.

Treatment

At the beginning it was decided to give penicillin by intramuscular injection of 25,000 units or 50,000 units six-hourly, the dosage being decided roughly by the size of the patient. Sulphonamides were not used, partly because they were thought to be unnecessary and partly because possible side-effects could mimic most of the complications of the treated disease. No local treatment of the ear was given apart from wiping away pus as necessary when it ran outside of the organ. Incision of the tympanic membrane was not considered. Bacteriological examinations were not made, the possibility that penicillin-resistant organisms were present being left to declare itself by failure of the treatment provided.

The results were assessed by simple clinical examination, general and local. So long as the signs and symptoms were improving, the treatment was persisted with until the patients' return to normal. No prescribed course or duration of treatment was attempted, results being the determining factor.

Results of Treatment

In all the 25 cases in which no fluctuation could be detected in the post-aural swelling there was a complete return to visible normality in from four to fourteen days. It was found that where the tympanic membrane was not ruptured the return to normal was quicker than when otorrhoea was present. Treatment was stopped when the aural region had regained anatomical normality, and not maintained until hearing had been regained. This occurred a little later.

At first it was expected that when fluctuation was present incision of the subperiosteal abscess would be required, but in some cases it decreased rapidly in size and was absorbed without any surgical intervention. Eventually resolution without surgical help occurred in 9 cases, but not in the remaining 16. In these 16 cases, if the size of the abscess was unchanged after a few days a trial was given to aspiration of the pus, but the rigidity of the walls prevented collapse and the cavity refilled with blood-stained fluid. Very soon it was decided that simple incision and drainage was preferable. After incision of the fluctuant abscess when necessary, the penicillin injections were continued, and rapid resolution usually occurred. Three cases retained a post-aural fistula for up to four weeks, and one case persisted for three months, eventually requiring a limited conservative mastoidectomy. One other case had mastoidectomy earlier. Ultimately, in all 50 cases a dry ear was produced, and in only one case was there a residual unhealed perforation.

Hearing.—With the younger children it was very difficult to decide about any residual deafness. The return of hearing was often delayed for a few days or weeks after the tympanic membrane had regained a normal appearance, but no permanent deafness was detectable at follow-up examinations up to about three months.

Failures.—It must be accepted that any recourse to surgical intervention is an acknowledgment that treatment by chemotherapy and antibiotics has failed. This occurred in 16 out of the 50 cases, and two of these eventually required limited conservative mastoidectomy. More important is the possible danger of failure owing to mistaken diagnosis. While this series was being collected one case was accepted for treatment, but the post-aural abscess increased in size, and when incised was found to contain foul pus. A review of the history revealed that otorrhoea had been present for a long time and the otitis was really a chronic lesion. Mastoidectomy revealed cholesteatoma. No harm had occurred from the few days' delay before operation; rather was the operation done with greater knowledge and under better circumstances than as an emergency. One other case, although suspected as tuberculous tympano-mastoiditis with a large fluctuant post-aural abscess and facial palsy, was given penicillin injections for two days before operation, and, far from coming to any harm, the facial palsy recovered. Subsequent tympano-mastoidectomy and streptomycin injections healed the lesion.

Original Opinion

On the evidence of this series it was accepted that acute mastoiditis in children could be cured in most cases by penicillin injections alone, with perhaps incision of the post-aural abscess when present; and, further, that there was no harm in trying this form of treatment even if mastoidectomy did eventually become necessary. The next step was to simplify the treatment by using the newly available preparations of penicillin which require injection only once daily. It was also hoped that by education and encouragement of the general practitioner in the need for early treatment of acute otitis media by antibiotics, and offering admission to hospital for this if requested, the incidence of mastoiditis would be lowered.

Follow-up of Cases

Of the original 50 cases it has been possible to follow up only 39, of which six were found to have slight but clinically detectable deafness. Of these six, three had either enlarged adenoids or sinusitis, and were referred for the appropriate treatment. Of the remaining three, one had had mastoidectomy originally as mentioned, and another had required this operation during a subsequent attack of tympano-mastoiditis. Among the 39 patients seen, seven had had further suppurative otitis media, which had settled under treatment.

Further Progress in Treatment

Up to the end of 1949 68 additional cases had been collected. These were treated in separate hospitals and there were variations in details of treatment, but 19 cases had penicillin injections of 300,000 units once daily, only two of them failing to return to normal. These two proved to be tuberculous tympano-mastoiditis, and required streptomycin and operation. It does seem, then, that the injection of 300,000 units of penicillin once daily, using the appropriate preparation, is adequate.

Among the 118 cases, there were 59 in which fluctuation was absent, and in all these resolution to normality was complete without any surgical intervention. In the remaining 59 fluctuation was present, and in 38 incision of the post-aural abscess was required; in the remaining 21 absorption of the abscess occurred naturally. Only three cases required mastoidectomy, and one of these was a tuberculous infection.

It is to be noted that the Hospital for Sick Children, Newcastle-upon-Tyne, admitted about 20 cases of acute mastoiditis in each of the years 1947, 1948, and 1949, and that there were only four cases during 1950. Probably this is to some extent due to the freer use of penicillin by the general practitioner now that it need be given only once daily.

Present Position

From the experience gained by study of over 100 of these cases I now make it a matter of routine to treat mastoiditis in children by penicillin injections, and at the moment 300,000 units once daily of the appropriate preparation is advocated. For reasons previously given, sulphonamides are not used, and incision of the tympanic membrane is deprecated.

When a case is first seen a careful history is taken to make sure, if possible, that one is dealing with a new acute infection; no immediate harm, however, will result from treating a chronic lesion, and the mistake will be revealed in the lack of progress later. Accurate recording of the local and general clinical picture is important as a basis for noting progress. The general state of the little patient may vary from very high fever to normality, and the first improvement under treatment should be reflected by a reduction of the former if present. Locally there will, of course, be evidence of otitis media with or without otorrhoea, and an evident post-aural inflammatory swelling, perhaps fluctuant. The presence of a facial palsy does not have any particular significance, but lymph-node enlargement usually indicates tuberculosis.

Once the penicillin treatment is begun the patient should be examined daily. Each sign or symptom, local or general, should begin to get better and disappear. A rapid improvement in the general condition and temperature is to be expected. In the course of a few days the post-aural swelling should show a reduction in size. When fluctuation is detected, if the abscess remains the same size for 24 hours it should be incised. If otorrhoea is present, and does not cease in about seven days, the pus should be examined bacteriologically for penicillin-resistant organisms, and appropriate action taken. No operations have been required for persistent otorrhoea in this series of cases. Should any new symptoms or signs develop during the course of treatment, all treatment should be stopped to allow of a free diagnosis. In some cases it has been found that external otitis has developed with pain and swelling, but has settled after cessation of the penicillin injections.

So long as all is going well the injections should be continued until the tympanic membrane regains a normal texture and the tympanum is air-containing. They can be stopped when a little deafness remains and a perforation is still unhealed. There is no prescribed period of treatment; it may vary from three days to three weeks, until the condition is cured. All cases should be followed up for about three months to be sure that hearing returns and that recovery is not retarded by other factors, such as enlarged tonsils and adenoids or sinusitis.

Summary

A survey is made of 118 cases of acute mastoiditis in children treated with penicillin.

In 59 cases in which fluctuation was absent resolution to normality occurred without surgical intervention.

In the remaining 59 cases fluctuation was present, and in 38 of them the post-aural abscess was incised. In the other 21 absorption occurred naturally.

Only three cases required mastoidectomy, one of them being a tuberculous infection.

The dosage of penicillin recommended is 300,000 units daily by intramuscular injection.

A CASE OF MYXOEDEMA DEVELOPING DURING *p*-AMINOSALICYLIC ACID THERAPY

BY

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As the result of the recent report of the Medical Research Council (*Lancet*, 1949) it is probable that the use of combined streptomycin and *p*-aminosalicylic acid (P.A.S.) therapy will be increasingly evident, and therefore it is of interest to report a complication that we have experienced during the past few months.

Case Report

The patient, a girl of 8½ years, was admitted to hospital on October 17, 1949, for the treatment of miliary tuberculosis and tuberculous arthritis of the right hip. At the onset she was given intramuscular streptomycin, but, as the second lumbar puncture revealed changes in the cerebrospinal fluid indicative of an early tuberculous meningitis, daily intrathecal streptomycin was begun. This treatment was continued without change until January 4, 1950, when P.A.S. was given in addition by mouth. At first the child had 9 g. daily, and subsequently (April 20) this was increased to 12 g. daily.

Under this regime her condition improved steadily, and she was discharged from hospital in July with a clear chest *x*-ray picture, a normal cerebrospinal fluid, and no evidence of disease of the hip. It was thought advisable at that time to continue the P.A.S. treatment, and the same dose was maintained. The child continued to attend at monthly intervals for *x*-ray examination of the chest and lumbar punctures, and she remained well until her visit on October 25, when her mother stated that she had been ill for a fortnight with fever, swelling of the face, loss of energy, and headache, and in addition she had vomited once or twice.

On examination the child looked sick; her face was puffy, and she had dry skin and hair; there was a firm diffuse enlargement of both lobes of the thyroid as well as the isthmus. Her pulse was slow, settling eventually between 60 and 70, her blood pressure was 80/60, and there was a soft localized apical systolic murmur. There were no other abnormal physical signs, but her mental state was unusual, as she was miserable, apathetic, and whining. She refused to co-operate with the nursing staff and was incontinent of urine and faeces.

Further investigations which were carried out on her re-admission to hospital were as follows:—Full blood count: haemoglobin, 70% (Haldane); red cells, 3,620,000 per c.mm.; white cells, 6,000 per c.mm. (polymorphs 60%, lymphocytes 28%, monocytes 9%, eosinophils 3%). Urine: nothing abnormal detected. Cerebrospinal fluid: protein, 35 mg. per 100 ml.; Pandy's reaction, negative; glucose, 70 mg. per 100 ml.; chlorides, 623 mg. per 100 ml.; cells, less than 3. Blood cholesterol, 250 mg. per 100 ml. Blood urea, 17 mg. per 100 ml. Serum potassium, 13 mg. per 100 ml. Glucose tolerance, impaired, probably because of temporary liver dysfunction. Prothrombin time, 40% of normal, using Rusven and Quick's methods. Radiograph of heart and chest: generalized cardiac enlargement but no evidence of miliary tuberculosis. Electrocardiogram: rate 64, inverted QRS and T waves in Lead III.

The P.A.S. therapy was stopped immediately and she was given menaphthone ("synkavit"), 10 mg. intramuscularly daily for three days, and then 10 mg. orally daily for one week. In addition, her diet contained large quantities of orange juice, and she was given a small amount of potassium citrate by mouth.

She was discharged home on November 8. Her general condition had improved considerably, her serum potassium was now 20 mg. per 100 ml. and her blood cholesterol 200 mg. per 100 ml.

When she attended the out-patient department a week later her pulse rate had risen to 90, the radiograph of her heart revealed a normal contour, and the thyroid gland had returned to normal both in size and in consistence. The most noticeable thing, however, was the improvement in her mental condition. She was much happier, very co-operative, and interested in everything that was going on around her.

She finally attended the clinic on February 26, 1951, when she was gaining weight and was happy and alert. Investigations, which included examination of the cerebrospinal fluid, estimation of blood cholesterol, *x*-ray examination of heart and chest, electrocardiography, and prothrombin time, were all normal.

We did not carry out an estimation of the basal metabolic rate, as the child was so uncooperative, but the clinical diagnosis of acute hypothyroidism was never in doubt. In fact, the picture was most striking, as was the rapid return to normal when the drug was stopped. Other complications of the therapy were hypopotassaemia and a prolongation of the prothrombin time, manifestations which have been described previously and which in this case disappeared in a very short time.

Comment

In the many careful reviews (Bogen *et al.*, 1950; Carstensen, 1950; Cayley, 1950; Madigan *et al.*, 1950) of the modern treatment of tuberculosis stress has been laid on the apparently innocuous behaviour of P.A.S.; the complications which have been detailed have included gastro-intestinal symptoms (nausea, vomiting, epigastric pain, and diarrhoea), pruritic dermatitis, neutropenia, and drug fever: in addition, bacterial resistance, prolonged clotting-time, and a lowering of the serum potassium, with the production of coupled heart beats and temporary muscle paralysis, have been described. Only one reference has been made to the thyroid gland—by Madigan *et al.* (1950), who suggested that the basal metabolic rate might rise during the administration of P.A.S.

It is true that the duration of P.A.S. therapy in this case was great, but it is quite conceivable that when the drug is used in the treatment of pulmonary tuberculosis this period of time will be exceeded, and it is suggested that the possibility of this complication should be entertained.

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A SIGN FOR DIFFERENTIATING UTERINE FROM EXTRAUTERINE COMPLICATIONS OF PREGNANCY AND PUERPERIUM

BY

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M.R.C.O.G.

A simple physical sign which does not appear to have been described before has been found useful in the differential diagnosis of abdominal pain in pregnancy and the puerperium. The test may have been employed by other clinicians, but the object of this communication is to submit to the profession my experience with the method so that its value in the hands of others may be proved or disproved.

The diagnosis of acute appendicitis complicating pregnancy is fully described in textbooks of obstetrics and discussed in detail in the classical monographs of Jerlov (1925) and Fahmy (1944). In *Queen Charlotte's Textbook of Obstetrics* (1943) it is stated; "It is important to define whether the chief tenderness is uterine or extrauterine. In the one case the lesion is probably concealed accidental haemorrhage, red degeneration of a fibroid, or an injury to the uterus, while in the other case it is liable to arise from a peritonitis or pyelitis." (To the causes of uterine tenderness, angular pregnancy may be added.) Fahmy says: "In order to palpate the appendix area more readily it has been suggested that examination be made with the patient in the left lateral position so that the uterus may move away towards the left side as far as possible." From these two statements it appears a logical step to include the "sign of fixed or shifting tenderness," described below, among the means of differentiation between the causes of abdominal pain in pregnancy and the puerperium. This sign bids fair to assist in diagnosing the cause of abdominal rigidity and tenderness in cases in which it is difficult or impossible to outline the uterus.

With the patient lying straight on her back, the examining fingers find the area of maximum tenderness to pressure on the abdominal wall. While the fingers remain in contact with that area without altering the intensity of pressure they are exerting to elicit pain, the patient is made to turn over on to the opposite side so that the plane of the anterior abdominal wall is approxi-

mately vertical. The pain produced by the pressure of the fingers will be less or will have entirely disappeared if the lesion is uterine and has fallen away from the examining fingers—"shifting tenderness" (concealed accidental haemorrhage, Case 3, or degenerated uterine fibromyoma, Case 4); pain sensation will be unaltered if the lesion is extrauterine—"fixed tendernesss" (due to appendicitis, Cases 1 and 2, renal or gall-bladder disease, ovarian cyst with twisted pedicle, diverticulitis).

It is obvious that this sign can be of use only if the uterus is large enough to be palpable abdominally, and that it may be misleading in the rare case in which a uterine lesion has become fixed by adhesions to the anterior abdominal wall (Case 4). In acute salpingitis, which does occur in pregnancy (Lennon, 1950), the result of the test will depend on the presence or absence of perisalpingitic adhesions.

No opportunity has arisen to diagnose a case of appendicitis or of twisted ovarian tumour during the puerperium, but the sign should be helpful in the differentiation of these and similar conditions from lesions confined to the uterus. In "puerperal endometritis," for instance, there is "shifting tenderness" (Case 6), and in a case of volvulus of the caecum (Case 7) tenderness was "fixed."

I have employed this method of examination for 10 years. A brief summary of seven relevant cases observed in recent months is appended.

Case Reports

Case 1.—A primigravida aged 22, 38 weeks pregnant; history of "labour pains" and vomiting for 20 hours. Rigidity and tenderness over the whole abdomen; maximum "fixed tenderness" in the right flank. No pus in the urine. Laparotomy. General peritonitis, perforated gangrenous appendicitis. Appendicectomy. Onset of labour two days later. Forceps delivery. Recovery.

Case 2.—A primigravida aged 23, 24 weeks pregnant; history of generalized abdominal pain for 60 hours, constipation, no vomiting. Rigidity and tenderness over the whole abdomen, maximum "fixed tenderness" in right iliac fossa. Laparotomy. General peritonitis, perforated gangrenous appendicitis. Appendicectomy. Recovery. Pregnancy preserved.

Case 3.—A 3-para aged 25, 38 weeks pregnant; history of severe generalized abdominal pain for three hours. The whole abdomen was rigid and extremely tender, so that the uterus could not be outlined. "Shifting tenderness" in both iliac fossae helped to arrive at the diagnosis of concealed accidental haemorrhage. Morphine and blood transfusion given; artificial rupture of the membranes after onset of uterine contractions, with some external bleeding. Foetus stillborn. Mother recovered.

Case 4.—A primigravida aged 43, 28 weeks pregnant; severe R.I.F. pain, vomiting, pyrexia. An extremely tender mass as large as an orange in the R.I.F. moved away from under the examining fingers when she was turned on to her left side—"shifting tenderness." A diagnosis of red degeneration of a uterine fibromyoma was made. The symptoms all but subsided with rest in bed. At 38 weeks the symptoms recurred; the findings were similar, but tenderness was now "fixed." Delivery by caesarean section. A subserous fibromyoma attached to the right uterine margin by a broad pedicle and adherent to the anterior abdominal wall was removed. Recovery. The diagnosis of red degeneration was confirmed histologically.

Case 5.—A primigravida aged 22, in labour, complaining of severe right-sided abdominal pain and of vomiting of 24 hours' duration. Temperature 100.2° F. (37.9° C.), pulse rate 132, guarding and "shifting tenderness" in R.I.F. There was no evidence of concealed accidental haemorrhage or of uterine fibromyoma. A diagnosis of appendicitis was rejected because tenderness was "shifting." Spontaneous delivery. Pain, vomiting, and "shifting tenderness" persisted. Laparotomy. In the peritoneal cavity there was free purulent fluid from which *Bact. coli* was cultured; the appendix was healthy; there was no Meckel's diverticulum. The right Fallopian tube was deeply congested, swollen, and its lumen contained pus; it was not adherent to any surrounding structure. Closure of the parietes without drainage. Chemotherapy. Recovery.

Case 6.—A 2-para aged 30, admitted with inversion of the uterus, which was replaced by taxis. Three days later there was pyrexia, vomiting, and pain in R.I.F. There was much tenderness of the right uterine margin; this tenderness was shown to be "shifting," and a diagnosis of "puerperal endometritis" was made. Chemotherapy. Recovery.

Case 7.—A 3-para aged 28; history of appendicectomy four years previously; immediately after spontaneous delivery excruciating pain in R.I.F. set in. There was "fixed tenderness" of a mass in the R.I.F., over which the percussion sound was tympanitic; it was impossible to outline the uterus. Laparotomy. The head of the caecum was bound down by a peritoneal band; the caecum, the lower half of the ascending colon, and the last 6 in. (15 cm.) of the ileum had undergone axial torsion through two full circles. The volvulus was untwisted after division of the peritoneal band. Recovery.

It is with pleasure that I express thanks for permission to publish to Mr E. C. P. Markby, Mr. J. W. Nankivell, and Mr. C. H. Vernon, under whose care these patients were admitted to the Royal Victoria Hospital, Bournemouth.

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Queen Charlotte's Textbook of Obstetrics, 1943, p. 157. Churchill, London.

A pamphlet describing some of the movements of population in England and Wales over the last 100 years or so has been issued from the General Register Office. The authors of it are Miss Mary P. Newton and Mr. James R. Jeffery. In the first part Mr. Jeffery describes the great migrations of people in this country after the industrial revolution. In 1851 about 50% of the population lived in rural districts, whereas in 1901 just over 20% did so. There was not at this time much movement between north and south, for most of the country dwellers moved to towns near their old homes. At the beginning of the nineteenth century Birkenhead had about 700 inhabitants. Sixty years later it had a growing population of over 50,000, while at the 1951 census its population was over 142,000. Though part of the great population increase in the towns during the nineteenth century was due to the general population increase in the country as a whole, the population in the large towns was increasing at a rate which was double that of the rest of England and Wales. By 1880 world competition economically depressed British agriculture, and again many agricultural labourers sought employment in the towns. Most of the immigrants to towns were young adults. In the second part of the pamphlet Miss Newton makes use of national registration statistics in analysing migration in recent years. An outstanding feature of migration to-day is the very high rate of movement experienced in holiday resorts. The greater part of this movement is not due to people taking holidays but to people employed in the hotels, boarding-houses, and catering industry. The pamphlet is *Studies on Medical and Population Subjects, No. 5: Internal Migration* (H.M.S.O., 1s. 6d.).

Medical Memorandum

A Case of Traumatic Rupture of a Complete Procidentia

The following case is rare enough and of such a bizarre nature as to warrant recording.

Case Report

A nulliparous spinster aged 61 had developed a uterine prolapse at the age of about 50: for the past two to three years she had had a complete procidentia, for which she had sought no treatment.

On the evening of February 2, 1950, she was struck on the chest and abdomen by the door of a taxi which was travelling briskly. It flung her backwards across the pavement and she fell heavily on her buttocks, and as she did so she felt something burst. Two policemen assisted her to her feet and took her indoors, where she sat on a chair and drank a cup of tea. Shortly afterwards bleeding was noticed and she felt very weak, so she was quickly conveyed to hospital.

On admission, some 20 minutes after the accident, she was found to be restless, and complained of lower abdominal pain. Her extremities were warm, the pulse was of good volume, and the blood pressure was 140/80 mm. Hg. Examination of the vulva revealed a total procidentia with marked keratinization: through a longitudinal tear, measuring 4 in. (10 cm.), in the prolapsed posterior vaginal wall and fornix there extruded 6–10 ft. (1.8–3 m.) of small intestine. There was no sign of damage to the gut or mesentery, bleeding from the vaginal edges was minimal, and palpation of the abdomen showed no abnormality.

Morphine, ¼ gr. (16 mg.), was given immediately and an intravenous drip transfusion set up. Thirty minutes later the patient was anaesthetized with thiopentone, gallamine triethiodide ("flaxedil"), and endotracheal cyclopropane. She was placed in the lithotomy position, and the bladder, which lay completely in the procidentia, was emptied by catheter. The abdomen was opened by a midline subumbilical incision. The main mesenteric pedicle, drawn down by the weight of prolapsed coils of gut, was seen to be disappearing through the floor of the pouch of Douglas. After thorough cleansing with saline, the gut was returned to the abdomen by manipulation from below and traction from above, and was found to be quite uninjured. After insufflation of penicillin and sulphathiazole powder the abdominal incision was closed without drainage. Simultaneously the vaginal rent was sutured in two layers from below, the peritoneum being closed as a separate layer. The procidentia was then replaced and a small vaginal pack inserted. During the operation, which took some 45 minutes, 1 pint (570 ml.) of blood was transfused. On return to the ward the patient's blood pressure was 150/90 mm. Hg.

Apart from a mild and transient paralytic ileus an uneventful recovery was made from this operation. During the ensuing days she was given 8,000,000 units of penicillin and her wounds healed cleanly. On February 21, nineteen days after the accident, the patient was allowed home.

Six weeks later she returned for treatment of the procidentia, which had completely prolapsed again. Next day the procidentia was replaced under anaesthesia, and a week later an extensive repair was performed. She made a satisfactory recovery from this operation and left hospital six weeks later.

Comment

Examination of the literature has failed to reveal a report of any similar case: rupture of the vagina itself, either normal or prolapsed, is not common, and extrusion of the intestines through such a rupture is even less common. It would appear that coitus injury is the commonest cause of rupture of the vagina, and many instances of this are fully reported in German, Mediterranean, and South American medical literature. Usually the injury is a simple tear of the vaginal wall, as in the case reported by Nicholls (1946). Sometimes the pouch of Douglas is opened; in Falk's case (1929) there was no escape of intestines, but Fischer (1929) reports a similar case, distinguished by "ausserordentlich heftiger Blutung," in which a coil of intestine prolapsed through the rent into the vagina. Prolapse of intestines into the vagina after rupture of the uterus is, of course, a well-documented accident, a dramatic example of which is the case reported by Sarnoff (1923), which ultimately recovered after resection of 15 ft. (4.6 m.) of intestine.

Surprisingly, traumatic rupture of a procidentia seems to be an unrecorded accident, at least in the literature of the past 30 years. Ulceration, usually due to constant friction or pressure, is, however, a not uncommon complication of total prolapse, and rupture of such ulcers is recorded. Movers (1940) records such a case with prolapse of omentum, the ulcer being due to erosion by a home-made pessary. Daley and Callum (1946) record a similar type of case, though the aetiology of the ulceration and rupture was not clear, in which extruded bowel was strangulated in the vaginal rent, and the patient died. Henkel (1929) also reports a remarkable instance: the uterus, retroverted and 12 weeks gravid, extruded through a ruptured pressure ulcer in the prolapsed posterior fornix, finally coming to lie upside down between the patient's thighs: recovery followed upon vaginal hysterectomy. Other serious complications recorded as affecting procidentia are incarceration (Thackston, 1943), and incarceration with strangulation of the contents of the hernia (Frank, 1938).

Apart from its rarity, the following points in connexion with our case seem worthy of comment: the absence of pain at the time of injury; the integrity of a full bladder lying within the procidentia; and the fact that the patient, an intelligent woman, was at no time aware of the nature and severity of her injury.

We are indebted to Professor P. B. Ascroft and Sir Gordon Gordon-Taylor for their advice and encouragement in the preparation of this paper. Our thanks are due to Mr. W. R. Winterton for his assistance in treatment.

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According to the *Daily Telegraph* of November 8, Lea Hurst, the house near Matlock, in Derbyshire, where Florence Nightingale spent much of her childhood and which remained in the hands of the family till 1940, has just been bought by the Royal Surgical Aid Society for conversion into a home for old people. It was previously a holiday home for nurses.

Reviews

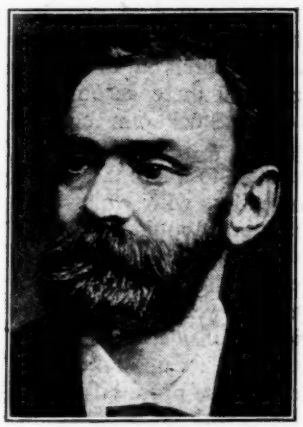
THE NOBEL PRIZES

BY

Sir HENRY DALE, O.M., F.R.S.

An English version[1] has been published of the jubilee memorial volume prepared for the celebration of the 50th anniversary, in 1950, of the great Foundation of Alfred Nobel. This took place in Stockholm on December 10, the anniversary of Alfred Nobel's death in 1896, and the regular day for the presentation by the King of Sweden of the Nobel prizes for science and literature awarded in each year. The always impressive and brilliant ceremony and following banquet were given on this occasion a commemorative character by an invitation to all the surviving earlier recipients of the prizes to be present.

The book, after an explanatory preface, begins with the remarkably short and concise text of the relevant section of the famous Will, dated in Paris on November 27, 1895. The interest on the remainder of the realizable estate — after family and personal bequests have been satisfied —is to be divided in five equal parts, to provide prizes to be awarded yearly to the persons judged to have produced in each year "the most important discovery or invention within the field of physics"; "the most important chemical discovery or improvement"; the most important discovery within the domain of physiology or medicine"; "in the field of literature the most outstanding work of an idealistic tendency"; and "the most or the best work for fraternity among nations, for the abolition or reduction of standing armies and for the holding and promotion of peace congresses." The whole residual estate, when realized, amounted to somewhat more than 30 million Swedish kronor, and the annual value of each whole prize, with some variations, has been of the order of £10,000. The peace prize is awarded by "a committee of five persons elected by the Norwegian Storthing," so that its award and presentation are entirely separate from those of the other four in Stockholm.



Alfred Nobel.

The Man

The first substantive chapter of the book is a biographical sketch of Alfred Nobel by the late Professor Henrik Schück, formerly president of the Nobel Foundation. It presents an attractive picture of the highly original, but not really eccentric, character of its subject. Nobel had genius in chemical invention and in the practical exploitation of its results, which brought him his large fortune. Born in Sweden and of Swedish parentage, he spent his boyhood from his ninth year in Russia, whither his father had migrated to establish an armaments factory, with fluctuating fortune. His two elder brothers became responsible, respectively, for oil developments at Baku and for another Russian armaments factory. Alfred, with an unsystematic and polyglot education, became widely international in his sympathies. He seems to have made Paris his main headquarters, though he built himself a house at Bofors, in his native Sweden, and died in his villa at San Remo. A bachelor and something of a recluse, he had a lively interest in literature as well as in science; and it would seem that, after Sweden, he felt himself more akin in sentiment to England and its language than to other countries. His only known poems, written at the age of 20, were in English, and he appears then to have been an enthusiastic admirer of Shelley.

He was never a public figure in any connexion while he lived; and an instinct for privacy, in a man of such genius and practical success, is apt to create legends. Making no profession of formal religious belief, he was reputed, in those censorious days of last century, to be an atheist; but he was beyond doubt a man strongly stirred by high and humane ideals, and a firm believer in a moral purpose in the history of mankind. "The advance in scientific research," he wrote, "and its ever widening sphere stirs the hope in us that the microbes, those of the soul as well as of the body, will gradually disappear, and that the only war humanity will wage in the future will be the one against these microbes."

The Foundation

The second chapter, on Alfred Nobel and the Nobel Foundation, is by Ragnar Sohlman, who was his close friend and associate and one of the executors of his will. It throws a wealth of additional light upon Nobel's life and character, and gives details of the long and complicated procedures required to make his will effective—negotiations and controversies with his relatives, the realization of the widely distributed investments and settlement of estate duties in many countries, and the granting of the necessary formal approval by the Swedish and Norwegian Governments. All these things took time, so that the Foundation could not come into effective being until September, 1900; and then the different bodies charged with the awarding of the prizes—the Swedish Academy of Science for physics and for chemistry, the Caroline Institute in Stockholm for "physiological or medical work," the Academy in Stockholm for literature, and the committee elected by the Norwegian Storthing for "champions of peace"—had all to accept their respective responsibilities, and required time to define these and to make provision for their fulfilment.

Then follow chapters on the procedures adopted by the different authorities concerned in the awards, during these first 50 years, of the prizes for literature, for physiology and medicine, for chemistry, and for physics. The amount of detailed information in these chapters is remarkable, and includes the mention of many cases proposed, and regarded by the relevant committees as worthy of prizes, but, for reasons discussed with great frankness, not chosen for awards in the final decisions. Of all these special chapters, the one on the medical

[1] *Nobel. The Man and his Prizes.* By H. Schück, R. Sohlman, A. Osterling, G. Liljestrand, A. Westgren, M. Siegbahn, A. Schon, N. K. Stahle. Edited by the Nobel Foundation. (Pp. 620. Kr. 48 or 65, according to binding.) Stockholm: Sohlmans Förlag. 1950.

prizes by Professor Liljestrand, the secretary of the committee of the Caroline Medical Institute, is by far the fullest, occupying 182 pages, in comparison with the 153, in all, given to both the chemistry and the physics prizes.

The medical chapter will obviously be the most interesting one to the readers of this *Journal*. In it will be found evidence of the special interest which Alfred Nobel, in his meetings with the late Professor Johansson in Paris in 1890, showed in researches having possible medical applications, and especially in the possibilities of preserving and transfusing blood. Here, also, will be found records of favourable but eventually ineffective decisions on the merits of many researches, including a number by our own countrymen. The names of such recently lost colleagues as Thomas Lewis and Joseph Barcroft, as well as of earlier friends and teachers, catch the attention in a merely cursory survey of this fascinating record. And nobody reading it—least of all, perhaps, one who has had the extraordinary fortune to be chosen for an award out of the array of those who have so clearly deserved it—can fail to be impressed by the large factor of chance by which such decisions must always and inevitably be affected.

Awarding of the Prizes

It seems clear that the committees, and perhaps the medical committee especially, have even increased the difficulties of their task, and limited their own freedom of decision, by the rules which they have made for themselves. Thus they have decided that the mention by the will of "discovery," as the reason for a prize, makes it necessary to select for award researches which can be held to have led to clearly definable discoveries, and not to choose more general contributions, however important and meritorious, to progress in a wider field. They have also decided not to take into consideration any claim which has not been proposed to them by one at least of the earlier prize-winners, or of the independent advisers in different countries, whom they specially invite in each year to submit proposals. Professor Liljestrand's article, with its engaging frankness, makes it quite clear that there have been cases in which his committee, acting upon their own unaided judgment, would have awarded a prize, or a share in one, had they not been prevented by the fact that no proposal for it had been made by any of their outside advisers. One can only admire such conscientious fidelity to a self-denying ordinance, even though one may share the doubts, to which Professor Liljestrand quite openly confesses, concerning its effect in certain instances. And it must be recognized after all that a committee might have reason to fear imputations of many kinds if, having so widely canvassed the world's opinions, they were in any year to reject them all in favour of one of their own.

It must, I think, be admitted that no committee nominated from a closed community, in accordance with the terms of the will, and called upon to choose one recipient of such a prize in each year, or not more than three to share it, from the large number of discoverers proposed by eminent advisers from all the world, could expect that its decisions would always command unanimous approval. But whatever mistakes may have been imputed to them by one or another, whether in awards which have been made or in failures to make others, nobody who can be regarded as a responsible witness has suggested that any such decision has been other than impartial and sincere. Adolf Hitler, indeed, chose to consider himself affronted by the Norwegian Committee's choice of a German recipient for a peace prize; and his characteristic reaction was to hurl an inclusive insult at all the committees, the four Swedish as well as the one Norwegian, by forbidding any German to accept a Nobel prize for any kind of achievement. As a result, the German nominees for the prizes in chemistry and medicine, awarded in 1939, were compelled to send letters of rejection. Professor Liljestrand's chapter gives an account, in some detail, of the arrest and the threats to which Professor Domagk was subjected because, while awaiting an official instruction with regard to its acceptance, he had acknowledged his receipt of the note informing him of the award for his discovery of the action of the sulphanilamide remedies. It was a great pleasure to see him, with Professors Kuhn and Butenandt, at the celebrations in 1950, though Hitler's action had deprived them all of their 1939 prizes beyond possibility of recall.

Independent Judgment

The chapters on the prizes for chemistry and physics, by Professors Westgren and Siegbahn, are similarly explicit in the information which they give about these awards, and about other claims considered but eventually not chosen. Nobody who reads all these accounts of the proceedings and decisions of the Stockholm scientific committees can fail to be impressed with the labour and the care which they have devoted to their tasks, and with the high sense of responsibility with which they have made their awards. And nobody could find, either in the record of the proceedings or in the resulting decisions, any ground for a suggestion that the members of any of the committees have been swayed in their choices by personal, political, or national considerations, or by anything but a firm determination to act upon their own unbiased judgment of the merits of the proposals before them. It can be stated, indeed, without fear of any challenge, that a general recognition of this scrupulous and independent attitude has given to these Nobel prizes for science a prestige in all the world of which they would certainly have been deprived by a suspicion of any kind of favouritism.

There are similar historical and explanatory chapters on the prizes for literature and for activities favourable to peace. In neither of these cases, however, is the awarding committee likely to be able to base its decisions on factual evidence submitted by proposers to the same extent as can those which award the prizes for scientific discovery. Opinion seems bound, accordingly, to figure more largely in these other decisions, which for that reason are more likely to give rise to dissent and controversy. But, again, I do not believe that anybody, except Hitler, has found reason to call into question the independence and sincerity with which these prizes for literature and for peace have been awarded.

Altogether this is a shining record, telling with courage and candour the story, first, of the plan which one of the world's great citizens made to encourage creative work for the material and moral betterment of mankind; and then of the faithful and conscientious endeavour made by those who have been charged with its administration to use to its full value what they have accepted as a sacred trust and a noble opportunity.

RADIOGRAPHY OF SMALL INTESTINE

Der Dünndarm im Röntgenbild. By Professor Fritz Kuhlmann. (Pp. 110; 80 figures. M. 11.80.) Munich: Urban and Schwarzenberg. 1951.

The small intestine is not an easy region for *x*-ray diagnosis, and this careful study, extending over twenty years, of the problems it presents is of practical interest and importance. The author first describes his methods, including the use of the Miller–Abbott tube, and illustrates his account with radiographs of the normal intestine. The comparison of these with photographs of the mucous membrane under similar conditions is most instructive. There follow discussions of abnormalities affecting position, motility, tone, and secretion, all illustrated by examples. Acute and chronic enteritis, ileus, and other special conditions are fully considered.

The volume shows the great advances that have been made in the interpretation of appearances in a difficult field. It is well illustrated by apt examples, and worth careful study by all who are interested in abdominal diagnosis.

HENRY SOUTTAR.

ART AND THE UNCONSCIOUS

Schizophrenic Art. Its Meaning in Psychotherapy. By Margaret Naumburg. Preface by Thomas A. C. Rennie, M.D. (Pp. 248; 63 illustrations, including 8 in colour. £3 10s.) London: William Heinemann Books. 1950.

There are grounds for the belief that certain recognizable elements are to be found in the spontaneous art of schizophrenics and that these are pathognomonic of schizoid psychology. Fragmentation, splits in design, rigid stereotypy, and the intermingling of writing with drawing, for example, are generally accepted as diagnostic signs. Miss Naumburg has been working under medical guidance for many years in this field of psychotherapy. Her main aim in the study of art productions has been to explore the conscious and unconscious causes of illness and thereby to secure therapeutic release and recovery. In addition she has attempted an interpretation of the symbolic meaning of the paintings and drawings.

A research project (which lasted for three years) at the New York State Psychiatric Institute on the use of art therapy in relation to early schizophrenia afforded an admirable opportunity for the author. But she has made only limited use of it. Two-thirds of the volume is devoted to a sensitive clinical study of two patients from the series investigated. While no final conclusions are drawn from this research, certain firm impressions were gained; art therapy is of therapeutic importance; its use increases the patient's capacity to express his inner feelings in words; the strength of the transference on the therapist is reduced and emotional dependence is small; emotional conflicts and their resolution move from the artist himself to the thing he creates, and he becomes aware that within him lies creative power.

The introduction is excellent. It provides a survey of psychotic and neurotic art from the descriptive studies of Simon (1876) and Lombroso (1895) up to the more penetrating work of Freud and Jung. Of special interest is the critical comment on the interpretation of symbols. The author shows clearly that the symbol has a very different significance in psycho-analysis and in analytical psychology.

E. A. BENNET.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Physical Basis of Life. By J. D. Bernal, F.R.S. (Pp. 80. 6s.) London: Routledge and Kegan Paul. 1951.

Prothrombin Deficiency. By R. Biggs, M.D. (Pp. 83. 10s. 6d.) Oxford: Blackwell Scientific Publications 1951.

Syllabus of Human Neoplasms. By R. M. Mulligan, M.D. (Pp. 317. 52s. 6d.) London: Henry Kimpton. 1951.

Cancer of the Colon and Rectum. By F. W. Rankin, B.A., M.A., M.D., LL.D., Sc.D., F.A.C.S., and A. S. Graham, M.D., M.S., F.A.C.S. 2nd ed. (Pp. 427. 55s.) Oxford: Blackwell Scientific Publications. 1950.

Psychosurgery. By W. Freeman, M.D., Ph.D., F.A.C.P., and J. W. Watts, M.D., F.A.C.S., F.I.C.S. 2nd ed. (Pp. 598. 77s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

Tuberculosis Among Children and Adults. By J. A. Myers, M.D., Ph.D. 3rd ed. (Pp. 894. 95s.) Oxford: Blackwell Scientific Publications. 1951.

The Ultimate Value. By Dr. R. Collis. (Pp. 181. 12s. 6d.) London: Methuen. 1951.

The Social and Biological Challenge of Our Aging Population. Proceedings of the Eastern States Health Education Conference, March 31-April 1, 1949. (Pp. 183. 18s.) London: Geoffrey Cumberlege. 1950.

Medical Neuropathology. By I. M. Scheinker, M.D. (Pp. 372. 75s.) Oxford: Blackwell Scientific Publications. 1951.

Chloroform. Edited by Dr. R. M. Waters. (Pp. 138. $2.75.) Wisconsin: The University Press. 1951.

Carcinoma of the Breast. By C. D. Haagensen, M.D. (Pp. 120. No price.) New York: The American Cancer Society. 1950.

Études Cliniques, Expérimentales et Thérapeutiques sur l'Allergie. Edited by Professor P. Vallery-Radot. (Pp. 239. 900 francs.) Paris: L'Expansion Scientifique Française. 1951.

Taschenbuch der Anatomie. By Professor H. Voss and Dr. R. Herrlinger. Vol. 3. 3rd ed. (Pp. 322. M. 10.) Jena: Gustav Fischer. 1951.

Über die Pathologie der Vegetativen Nervösen Peripherie und Ihrer Ganglionären Regulationsstätten. By Professor F. Feyrter. (Pp. 201. M. 24.) Vienna: Wilhelm Maudrich. 1951.

Klinik und Therapie der Magen-Darmkrankheiten. By Dr. F. Depisch. (Pp. 297. 28s. 6d.) Vienna: Springer. 1951.

Lehrbuch der Inneren Medizin. Edited by Professor K. Fellinger. Vol. 1. (Pp. 822. M. 38.) Vienna: Urban and Schwarzenberg. 1951

Die Wirbelverschiebung in der Lendengegend. By Dr. J. E. W. Brocher. (Pp. 98. M. 16.50.) Leipzig: Georg Thieme. 1951.

Fussgymnastik mit Kindern. By M. Scharll. (Pp. 14. M. 2.90.) Stuttgart: Georg Thieme. 1951.

Grundriss der Traumatischen Peripheren Nervenschädigungen. By Professor G. Bodechtel and others. 2nd ed. (Pp. 106. M. 10.20.) Stuttgart: Georg Thieme. 1951.

Praktischer Leitfaden der Beruflichen Hautkrankheiten. By Professor C. Carrié. (Pp. 186. M. 22.) Stuttgart: Georg Thieme 1951.

Medizinische Toxikologie. By Professor H. Fühner. 3rd ed. (Pp. 251. M. 21.60.) Stuttgart: Georg Thieme. 1951.

Multiple Sklerose und Schizophrenie als Syndrome bei Spurenelementmangelkrankheiten. By Dr. E. R. Elste. (Pp. 92 M. 5.50.) Stuttgart: Hippokrates-Verlag Marquardt. 1951.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY NOVEMBER 17 1951

CORTISONE IN OPHTHALMOLOGY

Last year Woods[1] was able to show that adrenocorticotropic hormone (A.C.T.H.) and cortisone quickly checked experimentally induced inflammation of the eye in the rabbit, thus giving a rational basis for clinical trial of these substances in acute ocular lesions. Biegel's histological studies[2] on uveitis induced in the rabbit by horse serum showed that cortisone inhibits inflammatory cell infiltration and the formation of plasmoid aqueous : his work also suggested that the effect is direct and local rather than a result of reduced general hypersensitivity. Evidence has also accumulated that these effects are transient, so that once A.C.T.H. or cortisone is withdrawn the inflammatory process becomes active again. These agents are therefore not curative in any strict sense: they are useful merely in regulating the severity of an inflammatory process—and whether it is desirable to check inflammation when it is often part of repair is not always a simple issue. In fact A.C.T.H. and cortisone have accentuated the problems forcibly brought into prominence by the sulphonamides and the antibiotics: What exactly is the nature of inflammation ? When is an inflammatory reaction useful, and when does it become harmful ?

These difficult problems are slightly less complex in ophthalmology, for an inflammatory reaction, though fundamentally protective and reparative, often has serious secondary consequences. This is clearly seen in acute iritis and iridocyclitis, when an unchecked inflammatory reaction will cause occlusion and seclusion of the pupil with secondary cataract and secondary glaucoma. It is for this reason that atropine and other mydriatics are so indispensable in ophthalmic practice. Even if they do not check the inflammatory reaction—and in all probability they do so to some extent—they at any rate prevent undesirable after-effects of inflammatory reaction at vulnerable areas. A.C.T.H. and cortisone, therefore, in reducing inflammatory reactions, make further therapeutic progress possible. But the essential question still remains whether it is desirable to check inflammatory reactions at all times and throughout the whole of the eye. This is no academic problem, as is shown by the conflicting reports on the effect of cortisone on wound healing, and by the fact that cortisone treatment may have grave consequences in tuberculosis by hindering fibrosis and so helping dissemination of the bacillus.

While there are fairly definite indications for the use of cortisone in acute iritis and iridocyclitis, uncertainty prevails with most other lesions. Acute iritis and iridocyclitis are only exceptionally the result of a removable cause. In most cases it appears that they must be regarded as the result of hypersensitivity of the tissues, possibly transient. Many of the inflammatory lesions of the eye are still of unknown origin, but when a causative agent can be traced and eliminated adjuvant treatment with A.C.T.H. and cortisone would still be helpful. When no such agent can be isolated definite indications for this treatment cannot be laid down without fuller knowledge and clinical experience. For instance, in scleritis it is a moot question whether suppression of inflammatory reaction may not lead to a staphyloma rather than to cure. If the indications for the use of A.C.T.H. and cortisone are as yet vague, there is rather more certainty about the method of use, though little certainty about dosage. Cortisone is one of the end-products of the activity of the adrenal cortex, unlike A.C.T.H., which excites the cortex to liberate cortisone as well as other hormones. Cortisone can therefore be used locally, while A.C.T.H. must be used systemically. As the side-effects of both cortisone and A.C.T.H. given by injection may be serious, and as the eye lends itself readily to local treatment, cortisone applied locally is the agent of choice in ocular therapeutics. Fortunately smaller quantities can be used in local therapy than are required for systemic treatment. Whether cortisone is best used in the form of drops or ointment, or as subconjunctival injections, is still to be decided, and there is as yet no agreement on dosage or frequency of application. Systematic studies on the intraocular concentration reached by these different methods have yet to come. Any assessment of the value of cortisone in ophthalmic therapeutics must at present be provisional, not only because of these considerations but also because of the fact that the period of observation after treatment has been relatively short.

In the United States a number of critical assessments of the value of cortisone and A.C.T.H. in ophthalmology have been published.[3] There is general agreement that cortisone is to be preferred,

1 *Amer. J. Ophthal.*, 1950, **33**, 1325.
2 *Arch. Ophthal., Chicago*, 1951, **45**, 258.
3 Ibid., 1951, **45**, 239–333; and Leopold, I. H., ibid., 1951, **46**, 187.
4 *British Medical Journal*, 1951, **1**, 1289.
5 Ibid., 1951, **1**, 1285.
6 *Brit. J. Ophthal.*, 1951, **35**, 672.
7 *Arch. Ophthal., Chicago*, 1951, **45**, 297.

and that it should be used locally. It is also agreed that cortisone quickly alleviates acute iritis and acute iridocyclitis; in chronic iridocyclitis the results are less definite, and recurrence has been noted. Acute interstitial keratitis quickly responds to cortisone, and favourable results have also been recorded in rosacea keratitis, disciform keratitis, episcleritis, and in spring catarrh, phlyctenular ophthalmia, and other allergic manifestations. The list of affections which have shown doubtful or no response is long: optic neuritis, retrobulbar neuritis, diabetic retinopathy, angio-spastic retinopathy, Eales's disease, senile macular lesions, glaucoma, Mooren's ulcer, the corneal dystrophies, retinitis pigmentosa, Tay–Sachs disease, sclerosing keratitis, keratoconjunctivitis sicca, most herpetic affections, mustard gas keratitis, and many more. In focal choroiditis it is possible that systemic therapy may have to be used. In this *Journal* Horne has confirmed the usefulness of cortisone in interstitial keratitis,[4] and Lavery and his associates[5] in other conditions.

Substantially the same conclusions have been reached by a Medical Research Council committee under the chairmanship of Sir Stewart Duke-Elder. The value of the report of this committee, published in the current issue of the *British Journal of Ophthalmology*,[6] is enhanced by a series of other contributions in the same issue. Ashton and Cook confirm the inhibiting effect of cortisone on wound healing—an effect proportional to the amount of cortisone used. Together with Langham they record partial inhibition of corneal vascularization induced in rabbits by the injection of alloxan into the anterior chamber—a finding also recorded by Lister and Greaves in corneal burns. Steen found that doses much in excess of those used clinically do not affect cells in tissue culture, while Cook and MacDonald, in studies on the blood-aqueous barrier, show that cortisone reduces capillary permeability. Sir Stewart's comprehensive clinical review is supported by his and Ashton's study of the significance of the latest experimental work. It would seem that in the immediate future several outstanding issues require to be settled by further detailed and critical studies. Both American and British experience suggests that cortisone may be valuable in the treatment of sympathetic ophthalmia. In all probability cortisone has a place in the treatment of post-operative inflammations—as distinct from infections. If early results, some of them distinctly questionable, are substantiated, cortisone may be useful in the treatment of retrolental fibroplasia. What exactly cortisone, with its dangers of delayed healing, will contribute to corneal graft surgery yet remains to be seen; if it helps to prevent vascularization by controlling an excessive inflammatory reaction it may prove a boon in a chancy operation. Whether or not cortisone may prove to be even more generally useful than atropine in ophthalmic practice will depend on the results of studies on the nature of inflammatory reaction, methods of administering cortisone, and pathological reactions of the eye. In a discussion at the Section of Ophthalmology of the American Medical Association in June last year Swan[7] gave the following warning, which still stands:

> Clinical trials with A.C.T.H. and cortisone have far outdistanced the experimental studies, largely because these drugs have offered the only hope for certain desperate conditions. Much remains to be determined about the dosage and side-effects, and the possibility of delayed or indirect detrimental effects has scarcely been investigated. It would seem wise if, for the present, use of these compounds were restricted to serious cases in which something would appear to be gained by the inhibition of excessive inflammatory reaction. There is no longer an excuse for the haphazard administration of these drugs for every recalcitrant ocular problem or as a substitute for accurate diagnosis and specific aetiological therapy.

THE DOCTOR–STATE RELATIONSHIP

"If you ask me what impression I have gained of the Whitley Councils, I say they have been utterly useless." This challenging observation was made by a regional hospital board witness before the Parliamentary Select Committee on Estimates.[1] Other witnesses were none too content with them either. One pointed out that hospital management committees are not represented on them, do not know what goes on in them, and sometimes feel that the awards "are made by people who do not really realize the implications of their decisions." And there were complaints that the employers' side is monopolized by the Ministry, though a Ministry official did not agree with this. Those who have negotiated in Whitley committees on behalf of various branches of the medical profession have also come to feel uneasy about the work of these committees. Many would probably agree with the conclusions of the Select Committee, which was considering Whitley machinery in relation to the hospital service. It was not satisfied that the Whitley committees work efficiently, and it drew attention to the fact that representatives of the Ministry of Health and the Department of Health for Scotland outnumbered representatives of the regional hospital boards. As a result, hospital authorities have not always accepted the Whitley decisions and some-

[1] See *Supplement*, p. 209.
[2] *British Medical Journal Supplement*, October 13, p. 141.

times have paid wages or salaries in excess of agreed scales. The Select Committee concluded by recommending that the Government departments concerned should urgently consider the application of the Whitley Council system to the hospital service.

The first Whitley Councils were established in 1918 in accordance with the recommendations of a Government committee presided over by Mr. J. H. Whitley, a former Speaker of the House of Commons. There was much industrial unrest in the preceding years, and the councils were designed mainly to bring together employers and workers in industry so that joint consultation might play its important part in what is in fact a joint enterprise. In its fourth report the committee recommended that a standing arbitration council should be set up, to which must be referred differences of principle and differences affecting whole industries, or large sections of them, when the parties failed to agree. An Act of 1919 gave legal effect to these recommendations by establishing the Industrial Court. Since then about 100 Whitley Councils have been formed, and the scope of the original idea has been extended in at least one important respect—namely, that the employers' side is sometimes not an independent person or company but the State. It is thus with the medical profession, and some of our difficulties spring from this peculiar relationship.

In that part of Whitley machinery where problems of the hospital service are negotiated—Whitley Committee B for medical men—representatives of Government departments over-weight the management (or employers') side, yet the Government as such does not employ the doctors concerned. It is the hospital boards who are the employers, and the Government officials have a prominent role because the Treasury pays the bill. The hospital board representatives may agree that the claims of their employees are just, while their fellow members from the Ministries may say that there is no money to meet them. Whereas in industry negotiations are straightforward, and if employers and employees do not agree the claim can go to arbitration, in the medical Whitley machinery the employers may agree, at least privately, to the rightness of a claim yet the management side as a whole refuse to concede it. The result is a feeling of frustration among the doctors and delay in negotiations. Alternative procedures should therefore be considered, and the Government's proposals will be awaited with interest.

If the Whitley approaches through the foothills to the Government redoubt are disquieting, so too are the powers with which the Government is armed. The Council discussed these at its meeting on November 7.[1] Statutory Instrument No. 1376 abolished the old arbitration tribunal and set up in its place another, and the First Interim Report of the Council[2] has emphasized the unsuitability to the medical profession both of the new tribunal's constitution and of the procedure governing disputes to be referred to it. Some have thought that an attempt should be made to have it annulled; but this is not necessarily the best course, for what the profession is seeking is an independent court of arbitration for the National Health Service, something quite separate from the new arbitration tribunal. The Council therefore decided as a first step to seek an interview with the Minister of Labour to discuss the matter with him before deciding what further action to take. The powers conferred on the Minister of Health by Order No. 1373, by which it seemed possible that he could repudiate agreements in the Whitley Council which he himself had approved, are also to be examined further, and he is to be asked to clarify them. An assurance will be sought, too, that there would be no interference of this kind with Whitley decisions.

To the traditional doctor–patient relationship the Health Service has added a second of which doctors have become increasingly suspicious—the doctor–State relationship. The Health Service in some form is here to stay, and so is the complex negotiating machinery characteristic of the modern State. But the doctor–State relationship is not yet free from the embarrassment that two mere acquaintances feel when they are suddenly thrown together in difficult circumstances. The relationship may become a satisfactory and settled one in time, but the forms in which it is at present expressed—mainly Whitley Committees and arbitration machinery—need careful scrutiny now.

DIABETES AND GROWTH

In his Sydney Ringer Memorial Lecture, which is printed in this week's *Journal*, Professor F. G. Young brings up to date the fascinating account of his researches in experimental diabetes which began over 15 years ago. It is a record of logical inference from careful observations, of hypotheses tested by careful experiments, which contrasts sharply with the inspired statements and fact-torturing theories which are sometimes heard in this context. Investigation of the diabetogenic properties of anterior pituitary extracts (A.P.E.) was begun in 1932 by Houssay, who had observed that hypophysectomy alleviated the diabetes induced in dogs by removal of the pancreas. Both he and Evans were able to induce diabetes in intact animals by injecting A.P.E., but later they found that consistent

results could be obtained only in animals in which the pancreas had been partially removed. This was a highly artificial condition, which bore little resemblance to the spontaneous diabetes of man. Young has had no difficulty in regularly inducing a permanent diabetic state in intact adult dogs and cats by means of A.P.E. The observation that crude extracts which were diabetogenic in the adult dog and cat exerted a growth-promoting effect in puppies and kittens did not prove that the two effects were due to a single hormone, and the possibility that the diabetogenic activity of Young's ox anterior pituitary extracts might be due to contamination with pituitary adrenocorticotropin could not be excluded until 1949, when preparations of growth hormone " of crystalline purity " became available.

It is now quite clear that a single agent is responsible for the stimulation of growth of immature animals and the development of diabetes in adult dogs and cats. Further, Young has shown that the action of A.P.E. in maintaining lactation in the cow parallels its diabetogenic activity in the dog. The rat, even when senile, responds to A.P.E. by growing, and never becomes diabetic. On the other hand, some puppies which are given daily injections of A.P.E. for a prolonged period cease to grow when they reach the stage of adulthood, and become diabetic. Young's view that growth and growth-hormone-induced diabetes are alternative responses to the same general metabolic stimulus is further supported by his study of the energy balances of rats and dogs receiving A.P.E. In both he found an increased deposition of protein and increased oxidation of fat. Glucose oxidation was inhibited, but, while in the growing animal this resulted in deposition of carbohydrate in the tissues, in the diabetic it caused hyperglycaemia and glycosuria. Milman and Russell's demonstration of the hypoglycaemic effect of growth hormone in normal rats favours the view that the hormone exerts its physiological effects in conjunction with an increased secretion of insulin. They suggest —and Young is in agreement with them—that a level of pituitary activity which would be appropriate to a period of growth (including foetal growth) or lactation might, if it occurred at a time when no such physiological outlet was available, lead to the pathological state of diabetes.

Important as these observations are for the light they shed on the endocrine control of growth and carbohydrate metabolism, their chief interest for the practising physician is their possible relevance to the aetiology of diabetes in human beings. Compared with the research worker in experimental diabetes, who is able to observe the changes that take place during the transition from a normal to a diabetic state, the clinician is at a disadvantage. He is presented with the end-result of a metabolic disturbance which may have been going on for many years, and is dependent on his patient's memory for his knowledge of the prediabetic period.

It is now well known that a proportion of diabetic women have a characteristic prediabetic obstetrical history, being unusually prone to give birth to exceptionally large babies. The suggestion that the high birth weight of the offspring is due to an excessive secretion of growth hormone by the maternal anterior pituitary gland is certainly more plausible than any other theory that has been advanced, and in the light of Young's work might well account also for the subsequent development of diabetes in the mother. Another clinical observation, first made by Priscilla White, in support of the diabetogenic action of the anterior pituitary in man is the excessively rapid growth which occurs in some diabetic children immediately before the appearance of diabetic symptoms. Any theory of the cause of diabetes must account for the obesity which precedes its development in over 50% of the cases. Young does not claim that obesity is necessarily caused by an excess of growth hormone, which is concerned with the storage of protein and carbohydrate rather than fat, and which could induce adiposity only indirectly through its action in stimulating the appetite. Though human diabetes has suggestive affinities with the experimentally induced diabetes of animals, it is clear that pituitary over-activity by itself fails to explain much which is mysterious in diabetes and cannot be regarded as the only factor of importance in the human disorder. The majority of acromegalics, for example, do not become diabetic, though they are subjected to intense and prolonged stimulation by the growth hormone, and it is likely that those who do are hereditarily predisposed to diabetes. Indeed, the genetic factor is the rock on which most aetiological theories founder. The exact nature of the deficiency which the diabetic inherits is unknown, but it is surely significant that pancreatectomy is the only certain method of inducing the disease in man and animals, though the diabetes to which it gives rise may be surprisingly mild in nature. It would appear that abnormal demands for increased insulin secretion, whether coming from the anterior pituitary gland or elsewhere, can be met by the pancreas of the majority of normal individuals, and that an inadequate pancreatic response is at least as important in determining the development of diabetes as the nature of the diabetogenic stimulus.

HYALURONIDASE AS A RESEARCH TOOL

Hyaluronic acid is generally considered to be an important, probably a major, component of the intercellular substance of mesenchymal tissues. We are as yet, however, profoundly ignorant concerning its metabolism, and the metabolism of the sulphate-containing mucopolysaccharides which in many sites occur alongside of it. The time is perhaps ripe for tackling the problem by the use of isotopic tracer elements, and a beginning has been made by Layton,[1] who has made a study of the incorporation of radioactive inorganic sulphate into organic esters, including chondroitin sulphate, by cells both at wound sites and *in vitro*. He claims to have shown that such incorporation occurs rapidly, and that cortisone inhibits esterification by heart and skeletal muscle tissue, but not by liver tissue.

There is, however, another tool to hand in the form of the enzyme hyaluronidase, of which partially purified and very active preparations are commercially available. Clinical uses of the enzyme were discussed in an annotation in this *Journal* recently (September 1, p. 536). This week we publish two complementary papers from the Canadian Red Cross Memorial Hospital, in which hyaluronidase has been used to explore the state of hyaluronic acid in the skin of normal subjects and of patients with rheumatic fever. Drs. E. J. Holborow and M. K. Keech (p. 1173) find no significant difference between the spreading effect of hyaluronidase in the two groups, although in patients under treatment with A.C.T.H. the spreading was definitely diminished. These findings are in agreement with recent work along similar lines in the U.S.A., although they contradict the original claim of Guerra[2] that the spreading effect of hyaluronidase is increased in acute rheumatic fever. The amounts of hyaluronidase which they used were large, when considered in terms of activity, and the time interval between injection and measurement of the area of spread of the indicator haemoglobin was long. Only very considerable differences in the state or concentration of the skin hyaluronic acid would be likely to be demonstrated, and secondary effects due to changes in rate of flow of fluid from capillaries to the tissue spaces, with the possibility of washing along the indicator haemoglobin, may have played a part in causing the day-to-day variations which they observed. The complication that most subjects became sensitized to the hyaluronidase preparation emphasizes a difficulty inherent in repeated tests with any potential antigen.

Dr. E. G. L. Bywaters and his colleagues (p. 1178) also studied the rate at which the changes produced in the skin by local injection of hyaluronidase are restored to normal. For 24 hours or more after injection of hyaluronidase, haemoglobin solution injected at the same site diffuses over a wider area than at an untreated site. After a period of time, which could be measured to within a few hours, haemoglobin diffusion was equal at treated and control sites. This time was taken to be that required for the hyaluronic acid depolymerized by hyaluronidase to be replaced or reconstituted, and the interesting observation was made that in patients with active rheumatic fever, and with Still's disease, the "reconstitution time" was significantly prolonged beyond that observed in normal controls or in tuberculous patients. The authors suggest that prolongation of the reconstitution time may reflect a deficient synthesis of ground substance.

Hyaluronidase is commonly used as a reagent for the detection of hyaluronic acid in histological sections. Metachromatic material, or a substance staining with the periodic acid-Schiff reagent, which is removed by treatment with hyaluronidase, is presumed to be hyaluronic acid. Such an interpretation is valid only if hyaluronic acid is the sole substrate for the enzyme preparation used, and it is perhaps insufficiently realized that testicular hyaluronidase preparations have also been shown to hydrolyse chondroitin sulphate (from hyaline cartilage, though not from skin[3]), a monosulphuric acid ester of hyaluronic acid obtained from the cornea, and unidentified sulphate-containing mucopolysaccharides from heart valves and tendon. For the specific identification of hyaluronic acid use of purified streptococcal hyaluronidase is probably safer,[4] although its specificity has recently been questioned.[5] Nevertheless, hyaluronidase remains a useful histochemical tool.

Hyaluronidases are in many ways tantalizing substances. Their production by many strains of virulent organisms (e.g., most pathogenic staphylococci, many group A streptococci, many pneumococci, and certain anaerobes), together with their occurrence in various snake and insect venoms, has encouraged the expectation that hyaluronidase and virulence would go hand in hand. A close correlation has, however, often been lacking—presumably because other factors are involved more important than ease of spread through connective tissue. Furthermore, study of the specific antibodies which are formed as a result of bacterial infection has invariably shown that such antibodies differ in behaviour very little from other antibodies formed simultaneously against other known bacterial antigens and exotoxins. Animal sera contain variable but considerable amounts of a non-specific inhibitor of testicular hyaluronidase, which is associated with the albumin fraction and is thought to be a mucopolysaccharide. The variations in non-specific serum inhibitor in disease, and in conditions of stress, have been studied by Glick and his associates. They find a rise in all such conditions, with a return to normal levels during convalescence, but no explanation is so far forthcoming. A whole number of the *Annals of the New York Academy of Science* (1950, 52, 943–1196) devoted to "The Ground Substance of the Mesenchyme and Hyaluronidase" testifies to the amount of work done with hyaluronidase, but the significance of much of it remains tantalizingly around the corner.

1 *Proc. Soc. exp. Biol., N.Y.*, 1951, **76**, 596.
2 *J. Pharmacol.*, 1946, **87**, 193.
3 Meyer, K. & Rapport, M. M., *Fed. Proc.*, 1950, **9**, 205.
4 Rogers, H. J., *Biochem. J.*, 1948, **42**, 633.
5 Crowley, N., *J. gen. Microbiol.*, 1951, **5**, 239.

RADIATION CANCER OF THE PHARYNX

Dr. A. W. G. Goolden's article last week (November 10, p. 1110) on radiation cancer of the pharynx is of exceptional interest. As he states in his review of the literature, though there have been many examples of radiation cancer of the skin the occurrence of radiation tumours in the deep tissues is rare. Of his four cases at least three seem to be very convincing. All three were in women; two had a post-cricoid carcinoma and one a carcinoma of the pyriform fossa. All three had received radiation treatment of the neck for thyrotoxicosis some 26 to 29 years previous to developing a cancer of the pharynx; thus there was a long latent period in each case. In all three there had been severe radiation damage to the skin; in two the damage was so severe as to necessitate repair by skin grafting. Histological examination showed malignancy in all three cases and squamous carcinoma in two cases; while in the third, a case of post-cricoid carcinoma, the condition was unusual in that it was a fibrosarcoma. As is pointed out by the author, however, radiation tumours do often display some abnormality in histology or site. The fourth case described is not so convincing. The patient was a woman who developed a squamous carcinoma of the posterior wall of the hypopharynx. She had received radiation treatment some 30 years previously for tuberculous glands of the neck. There was therefore a long latent period, but in this case there were no radiation changes in the skin and it is therefore, as the author states, doubtful if this should be regarded as a radiation tumour; the site of the tumour, the posterior wall of the hypopharynx, is uncommon. In a case of this kind it is a reasonable supposition that radiation, though not solely responsible, may possibly have acted as a contributory factor in a subject with a predisposition to cancer.

Yet the following fact should be borne in mind. To be more certain that these were true radiation tumours, it would be necessary to make a very large-scale investigation on all cases treated by radiation some 20 to 30 years ago for any benign condition in the neck. It would then be possible to ascertain whether the incidence of cancer of the throat in these cases was higher than the normal incidence. It is, of course, not possible to get any accurate details of the radiation technique used so long ago. At that time there were no accurate methods of dosage estimation and indeed there was no recognized unit of dosage. With modern equipment and modern technique very accurate estimation of dosage is possible. The very protracted course of the treatment is an important factor in causing the carcinogenic effect—small doses were given constantly over periods of time lasting as long as six to nine months. It should be noted that in present-day radiation treatment this very protracted technique is no longer used.

In conclusion, it is perhaps important to stress that the occurrence of radiation tumours of this kind is no contraindication to the use of radiation in the treatment of thyrotoxicosis or tuberculous glands of the neck, when by modern techniques the dosage is carefully controlled and is not sufficiently high to produce damage to skin or other structures. Neither, of course, is the existence to-day of such radiation tumours any argument against the radiation treatment of malignant disease in general, even when nowadays, though very protracted techniques are not used, the dose must sometimes be carried to a level where skin damage is produced. Most patients treated for cancer are well past middle age, and a primary growth to be treated by radiation is obviously more serious than a possible cancer arising after a further period of some 20 or 30 years.

BANTHINE AND GASTRIC ACIDITY

Since the demonstration that section of the vagus nerves causes the healing of various kinds of peptic ulcer, attempts have been made to find a substance which would effectively block the transmission of vagal impulses and so achieve the same therapeutic result without operation. The claim has been made that "banthine" is such a substance: it is the methyl chloride of diethylaminoethyl xanthene-9-carboxylate hydrochloride, and thus it is a quaternary ammonium compound. Grimson, Lyons, and Reeves[1] have tested it in 100 patients, giving usually 100 mg. at six-hour intervals. The effect of the drug was determined by *x*-ray examination, and when there was evidence that the ulcer had become smaller after three to eight weeks the patients, who were encouraged to return to work during treatment, were permitted to reduce the dose by half. Five of the patients were treated surgically five to ten weeks after the banthine administration had begun, so that in these it failed. The authors consider, however, that, but for the use of banthine, operation would have been needed in 55. They ascribe its beneficial effect in the main to the reduction in gastric motility rather than to a reduction in the volume and acidity of the secretions, for they found these were less affected than by section of the vagi. Side-effects were dryness of the mouth, less troublesome after the first few days, dilatation of the pupils, some constipation, and decrease in the force of urination. Smith, Woodward, James, and Dragstedt[2] have made observations on dogs with gastric pouches and recorded a reduction of 17% in one dog and 42% in another in the 24-hour secretion of acid. Giving 100 mg. of banthine by mouth to six patients every four hours, they found a reduction of 30–86% in the nocturnal acid secretion. No serious side-effects were noted with this dosage.

The most objective study of banthine seems to be that of Benjamin, Rosiere, and Grossman,[3] who set out to compare its action with that of atropine, since atropine is the best drug up to the present for depressing vagal impulses. They also observed its effects on dogs with gastric pouches as well as on patients. They found that both banthine and atropine depressed the basal gastric secretion and also the secretion evoked by histamine, though the latter was only partially inhibited. Weight for weight, atropine was about eight times as

[1] *J. Amer. med. Ass.*, 1950, **143**, 873.
[2] *Gastroenterology*, 1950, **15**, 718.
[3] Ibid., 1950, **15**, 727.
[4] Abstracts 18th Internat. Physiol. Cong., 1950, p. 239.

potent as banthine. Moreover, since doses of banthine and atropine which depressed the gastric secretion to the same extent also had the same effect on the pulse rate, they conclude that the action of banthine is essentially like that of atropine, paralysing the terminal endings of the vagus in the stomach wall. Thus banthine does not owe its main effect to a blocking action on the vagal ganglia, though it has some effect of this kind. What remains to be explained is the diminution which atropine causes in the secretion due to histamine. Recently Grossman[4] has described experiments in dogs with the stomach divided into two isolated pouches, pyloric and fundic. When the pyloric pouch is irrigated with a 0.5% solution of acetylcholine the fundic glands secrete acid. Their experiments have led Grossman and his colleagues to the view that acetylcholine is constantly released at the parietal cells and increases the sensitivity of these cells to histamine. When atropine is given this action of acetylcholine is excluded and the effect of histamine is thereby inhibited. It may be concluded that there is no clear evidence that banthine is superior to atropine, since the side-effects have been found to be very similar with both. However, the authors are prepared to admit that banthine may have an effect in peptic ulcer by some action other than inhibition of secretion; thus it may be superior to atropine as an antispasmodic.

CIVIL SERVICE DOCTORS

The poor financial prospects for doctors in the Civil Service have for some time deterred possible applicants. The report of the Howitt Committee[1] will not improve matters. Indeed, if it is accepted by the Chancellor of the Exchequer, the country will be fortunate if it does not soon lose some of its Civil Service medical officers by resignation. The claims of these doctors were put before the committee by a Joint Committee of the B.M.A., the Institution of Professional Civil Servants, and the Ministry of Health Medical Staff Association.

There are about 650 medical officers employed in 18 Government departments. Though they compose a small branch of the medical profession, many of them occupy key posts. Recruitment to them has for some time been difficult. This is unfortunate in view of the great importance of these posts now that the National Health Service is in being; and, as we warned last year,[2] many Government departments are seriously short of doctors. The report acknowledges that "for some time past the service has not been able to attract to the medical officer and senior medical officer grades a sufficient number of recruits of the required quality." Recruitment is still not satisfactory, and "these circumstances suggested that the prevailing rates of pay might be too low." Yet the committee's recommendations to make the posts attractive are merely trifling. At present the medical officer starts at £1,250 linked to age 38. The committee proposes that the age should be 35. The maximum remains the same at £1,725. To attract men and women with exceptional qualifications or experience to apply for special posts the committee recommends a starting salary of £1,500 linked to age 35 with the same maximum of £1,725. Senior medical officers now start at £1,725, rise to £1,800, and thence by £100 increments to £2,000. The committee's only recommendation is that salaries should begin at £1,800 and rise by £100 increments to £2,000. Even though Civil Service doctors have superannuation benefits to the cost of which they do not contribute, it is impossible to imagine such small changes as these having the slightest effect on recruitment.

The committee's opinion on the kind of service it has in mind seems to be clearly reflected in its statement that "it is not necessary that the remuneration of the Civil Service medical staff should rival that of the most successful doctors outside the Civil Service." According to the committee, the salaries should be "such as will attract to and retain in the service doctors of adequate quality who are interested in the kinds of work to be found in the service . . ." and it is content to advocate salaries that are second-best when the Civil Service ought to be attracting men of the highest quality for these important posts. In negotiations on behalf of all other branches of the profession during the last two years, the Spens reports, though applying only to two branches, have inevitably been the background to discussion, because so many doctors are now paid by the State; and each branch of the State services must compete with the others for its staff. The Howitt Committee claims to have taken into consideration the rates of pay of those doctors outside the Civil Service, and claims that these "must to a great extent influence the salaries" paid within it. Unfortunately the influence on its recommendations appears to be so meagre that even now the Civil Service salaries will not successfully compete with the claims of the other branches of the profession.

[1] *Report of the Committee on Pay and Organization of Civil Service Medical Staffs.* H.M.S.O.
[2] *British Medical Journal*, April 22, 1950, p. 946.

A GIFT FROM SOUTH AFRICA

One of the pleasant ceremonies at the Council Dinner in the Great Hall of B.M.A. House on November 6 was the presentation to the Association of a South African flag. Dr. A. L. Geyer, High Commissioner for South Africa, making the presentation on behalf of his Government, spoke of the debt which South Africa owed to British medicine, and said that the flag was a mark of appreciation for the services rendered by the Association to his country. Dr. E. A. Gregg, Chairman of Council, after referring to the disappointment felt by members of the Association that circumstances had prevented them from holding their Annual Meeting this year in South Africa, warmly thanked Dr. Geyer for this gift.

The next session of the General Medical Council will begin on Tuesday, November 27, at 2 p.m., when the President, Professor David Campbell, will take the chair and deliver an address.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

TREATMENT OF WATER AND ELECTROLYTE DEPLETION

BY

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In a previous article in this series entitled "Modern Views on Uraemia and Dehydration" *(British Medical Journal,* 1950, **1**, 893) I gave a general description of the treatment of dehydration. The present article aims at a more detailed exposition of the treatment of water and salt depletion, and includes an account of potassium depletion.

Water Depletion

Here the water content of the body is reduced both absolutely and relative to the salt content, and the concentration of electrolytes in body fluids, as estimated by the serum-sodium level, is increased. The syndrome arises when the intake of water is impeded by dysphagia, apathy, or coma, and is aggravated by any increase in sweating, as in the febrile patient. Hyperpnoea increases the loss of water in the expired air.

The characteristic subjective symptom of water depletion is thirst, which is related to general tissue dehydration and is not relieved by moistening of the tongue and palate. Oliguria is an important sign of an inadequate water intake, but must be distinguished from the oliguria of advanced salt depletion or primary renal disease. The urine in water depletion is of high specific gravity and chloride concentration. General signs of "dehydration," such as wrinkling of the skin, collapsed veins, and low intraocular tension, are less obvious in water depletion than in salt depletion of comparable degree, for the fluid loss is spread over the whole body fluid, not limited to the extracellular fluid compartment as in salt depletion. Water depletion requires treatment with non-saline fluid; suitable fluids are discussed later.

Salt Depletion

The primary change in salt depletion is decrease in the total salt content of the body. Salt is the definitive electrolyte of extracellular fluid, and a deficiency of salt causes shrinkage of the extracellular compartment, though the absolute fall in extracellular fluid volume is minimized by some lowering of the concentration of salt in the remaining fluid.

In contrast to water depletion, which arises mainly from defective fluid intake, salt depletion is usually due to abnormal losses of salt, though it may on occasion be aggravated by defective intake of salt in patients with anorexia. Vomiting, diarrhoea, intestinal aspiration, and exudation from extensive burns are all obvious causes of loss of salt from the body; the urine may be a less obvious channel of salt loss, as in Addison's disease or diabetic pre-coma, in both of which severe salt depletion can be traced to salt loss in the urine. Copious sweating is another cause of salt loss from the body, but water is lost to a greater extent than salt, and symptoms of salt depletion arise only when thirst is satisfied by water without added salt.

Review of the causes of the two syndromes indicates that salt depletion, as a syndrome demanding active treatment, is commoner than water depletion, or, at least, that in the mixed syndrome of clinical dehydration salt deficiency usually predominates over water deficiency.

General signs of dehydration are prominent in salt depletion, and it may be very difficult to get into the collapsed veins, either for sampling or for venoclysis. Thirst is often rather strikingly absent. The urine volume may be quite high in mild salt depletion, but oliguria supervenes when the plasma volume has shrunk and the blood supply to the kidneys has decreased. The urine is usually chloride-free, except in Addison's disease or acidosis, and the plasma sodium is low; these points serve to differentiate the oliguria of advanced salt depletion from that of water depletion. Vomiting and anorexia may occur in salt depletion, and add to the difficulty of treatment with saline fluids.

Acidosis and Alkalosis

Disturbances of acid-base balance are often found in association with depletion of body fluid. Gastric juice contains more chloride than sodium, and its loss promotes alkalosis; intestinal juices are alkaline, and their loss by aspiration or diarrhoea leads to acidosis. Excessive breakdown of body fat, as in starvation or uncontrolled diabetes, promotes an organic acidosis. Acidosis may also be produced when salt depletion is treated by sodium chloride alone; such treatment dilutes the plasma bicarbonate, giving rise to a "dilution acidosis." Clinically, acidosis is associated with air-hunger, and the urine may contain chloride even when there is clear evidence of salt depletion. A low alkali reserve is found in this type of acidosis. Alkalosis is often quite silent clinically, but unusual drowsiness or mental aberration may suggest it, and polyuria is not uncommon; the alkali reserve is high.

Biochemical Tests in Diagnosis

Unfortunately, biochemical tests do not give direct estimates of the total amount of salt and water in the body, but only of concentration of electrolytes in body fluid. A further limitation is that only the extracellular fluid, as represented by plasma, is directly accessible to analysis. As a general rule, however, salt depletion is attended by a lowered concentration of sodium and chloride in the plasma, and water depletion by an increased plasma sodium. But it sometimes happens that concentrations of electrolytes give a false picture of electrolyte balance in the body, usually because the kidneys have failed to respond by appropriate changes in salt and water output. For this reason among others biochemical results must form only a part of the evidence on which clinical decisions on salt and water depletion must be based; a history of the type and amount of fluid lost is just as important as the biochemical results. When a general diagnosis has been arrived at on the sum of evidence, biochemical results are valuable in assessing the degree of depletion, with a view to replacement therapy.

The plasma sodium is the most satisfactory single estimation, especially when it can be done quickly and accurately by a flame photometer. The normal range is 137–147 mEq per litre. When a flame photometer is not available the plasma chloride and plasma bicarbonate should be estimated on the same sample. The plasma chloride is normally 100–105 mEq per litre, and the plasma bicarbonate 25–30 mEq per litre. When the sum of chloride and bicarbonate is outside the range of 125–135 mEq per litre an abnormality in plasma sodium can be inferred. Deficit of plasma sodium is confirmatory of salt depletion and gives an estimate of its severity. For a patient of average size a deficit of 10 mEq per litre of plasma sodium is equivalent to a total body deficit of 500 mEq of sodium, equivalent to about 30 g. of sodium chloride. The plasma sodium (or chloride + bicarbonate) gives information on the "water/salt ratio" in the body.

It is often desirable to know whether acidosis or alkalosis is present, and the plasma bicarbonate is the critical investigation here—a low figure suggesting acidosis and a high one alkalosis. Respiratory acidosis or alkalosis must be excluded clinically before basing an assessment of acid-base balance on the alkali reserve, but they are uncommon by comparison with metabolic acidosis and alkalosis.

The blood urea also gives some information on the severity of salt or water depletion if primary renal disease can be excluded; this may be useful in those few patients in whom salt depletion is associated with normal electrolyte levels in the plasma—a raised blood urea is then valuable supporting evidence for a clinical suspicion of salt depletion.

The significance of the plasma potassium will be discussed in relation to potassium depletion.

Choice of Fluid for Treatment

When it has been decided that body water is depleted to a greater extent than salt, the appropriate fluids for use in treatment are water by mouth or 5% glucose intravenously or subcutaneously. In the alert conscious patient who is not vomiting, the water intake by mouth should be pushed until thirst is relieved; thereafter it should be adjusted to some 1,500 ml. a day, or 2,500 ml. in the presence of fever or hyperpnoea. When the patient cannot be roused to drink adequately, or when he is vomiting, 5% glucose can be given parenterally, or a rectal drip of tap-water can be set up. When a patient who has previously been thirsty no longer complains of thirst, it is a sign that the water depletion has been substantially corrected, and the fluid intake should be adjusted to basal requirements.

When the patient's kidneys are healthy no real harm is done by giving some excess of water, as the excess will promote a corrective water diuresis; but the situation is quite different when the kidneys are faulty, so that they cannot respond by water diuresis to excessive water intake. Water intoxication is then a real danger, to be avoided by giving just enough fluid to control thirst.

For a few days after surgical operation water given to the patient is excreted abnormally slowly, and apathy, retching, or convulsions may then be signs of excessive water ingestion. A low serum sodium, in the absence of dehydration, is biochemical evidence of some degree of water intoxication. The intake of water should be restricted, and sweating encouraged by radiant heat cradle. Actual convulsions can be controlled by hypertonic saline injected intravenously—10–20 ml. of 5% saline is given by syringe.

Correction of salt depletion has to be done with saline fluids. Unfortunately, only fluids of quite low salt content can be tolerated by mouth in any quantity; patients with salt depletion, moreover, do not have a craving for salt comparable to the thirst of a patient with water depletion. Something can be done by adding salt to the food over a period of time, and by using drinking water, milk, fruit drinks, or meat extracts made up to a salinity of about 0.45% sodium chloride ("half normal"). But it is not possible to correct severe salt depletion rapidly by oral saline fluids, as rapid correction of salt depletion demands fluids of a higher salinity than body fluid.

The size of the salt deficit in clinical salt depletion has not always been realized, but it constitutes a real difficulty in replacement therapy. For example, a deficit of 20 mEq per litre in the plasma sodium, such as is by no means uncommon in clinical salt depletion, corresponds to a total body salt deficit of 1 gramme-equivalent—that is, no less than 58.5 g. of salt or about 7 litres of "normal saline." It is obvious that a deficit of this order cannot be quickly corrected by mouth, and, further, that its correction by normal saline involves the giving of very large amounts of fluid by vein.

In patients with unequivocal salt depletion we have found it advisable to correct the greater part of the initial deficit with 2% or 5% saline, allowing the patient to drink at will during the infusion; we have even given as much as 500 ml. of 10% saline in this way, without untoward effect, and there is much less risk of overloading the circulation when this comparatively small amount of fluid is given. An infusion of this type should be spread over about three hours. After gross salt deficit has been partly corrected, and the kidneys have been assured of an adequate circulation, it is possible to complete correction of the deficit and to cover basal requirements of salt by the use of normal or half normal saline. At this stage it is important to watch for signs of overdosage with salt; such overdosage leads to expansion of the extracellular compartment, including the plasma volume. Engorgement of the veins or moist sounds at the lung bases are clear indications for stopping intravenous saline.

In patients who cannot take or retain water by mouth, and in whom therefore hypertonic saline therapy may carry some risk, the best course is to aim at a more gradual replacement of the salt deficit with normal saline, by giving 3–5 litres a day for two or three days and watching closely for any signs of saline overloading.

Special caution must be exercised in treating salt depletion in infants and children, since the absolute salt deficit is small because of the low body weight and also because of the inability of the infant kidney to attain a high concentration of urinary chloride; in the adult the ability to form a hypertonic urine is a partial protection against overdosage with salt. On the other hand, the daily turnover of water in infants is high in relation to their weight, by comparison with adults, and 0.2% or 0.45% saline should be used in the treatment even of salt depletion.

No reference has so far been made to the control of the acid-base balance during treatment with intravenous fluids. If water and salt balance is restored and maintained, healthy kidneys can usually correct acidosis or alkalosis of moderate degree. As has already been men-

tioned, when large amounts of sodium chloride are given there is a tendency to acidosis; for this reason, when the patient has no antecedent alkalosis it is wise to give a fifth part of the sodium replacement in the form of bicarbonate by mouth, or lactate by vein. Sodium lactate is usually supplied in ampoules of molar concentration, and should be diluted one part in six to make M/6 sodium lactate, which is isotonic with plasma.

In the treatment of primary severe acidosis M/6 sodium lactate should be used; the alkali reserve should be estimated frequently, as kidney function may be impaired, and with it the defence against alkalosis from overinfusion of lactate.

The appropriate treatment for primary metabolic alkalosis depends largely on the cause. When vomiting is paramount the alkalosis is associated with severe salt depletion and can be corrected by replacement of the salt deficit by sodium chloride without lactate. When the alkalosis is related to long-continued alkali treatment of peptic ulcer there is no salt deficit and ammonium chloride can be used by mouth. The use of M/6 ammonium chloride intravenously has been recommended for the treatment of alkalosis, but it should be limited to patients with a severe primary alkalosis and with no salt depletion.

In treating electrolyte imbalance we must always remember that the agents used are themselves capable, when given in excess, of causing a syndrome opposite to what is being treated. It is not enough merely to make even a careful initial assessment of the original water or salt deficit and to restore it quantitatively; not only is the error of any such assessment considerable, but the body also adapts itself to water or salt depletion, and simple restoration of a calculated deficit will not restore normality but will leave the body economy distorted by such adaptations as have taken place during the period of uncorrected depletion. Fortunately, with each approach to normality the natural homoeostatic capacities of the kidney are liberated from the constraints imposed on them by the severer degrees of fluid depletion and they can correct considerable deviations from the optimum of fluid given. This does not absolve us from the responsibility of making a careful initial assessment and of keeping constant observation and undertaking biochemical control so long as fluid is being given artificially.

When the patient has been adequately treated for water or salt depletion his weight should be normal, and there should be no oedema or venous plethora, no haemoconcentration, and no abnormality in the plasma concentration of sodium, potassium, chloride, or bicarbonate. The blood urea should be falling, though it often takes some days for an accumulated nitrogen load to be dissipated.

Potassium Depletion

The widespread recognition of potassium depletion as a clinical problem is a matter of the past five years, and springs from increasing appreciation and extension of Darrow's fundamental observations on potassium depletion in infantile gastro-enteritis. Although potassium depletion is probably as common as sodium depletion, it is much less easy to demonstrate, as potassium is mainly an electrolyte of intracellular fluid; severe potassium depletion may be present without any clear change in the potassium concentration in plasma. It is true that potassium depletion can be shown by analysis of muscle biopsy material or by subsequent retention of potassium in a balance experiment, but these methods are limited in their application and to some extent retrospective. It is the more important to appreciate the usual mechanisms by which potassium depletion is produced, so that treatment may be started early.

The body depends for its potassium intake on ingested food—notably bread, vegetables, and meat—and any restricted diet is likely to be a low-potassium diet; anorexia likewise lowers the potassium intake. The renal defence of body potassium is relatively inefficient, in that potassium is excreted to some extent even on a low-potassium diet, in rather striking contrast to the disappearance of sodium from the urine on a low-sodium diet. The renal loss of potassium is increased by dehydration, by massive saline infusion, and by osmotic diuresis such as is produced by the glucose excretion in uncontrolled diabetes mellitus. Trauma to tissue raises the plasma potassium and augments urinary potassium excretion. Urinary output of potassium is also increased under the influence of adrenocorticotrophic hormone, cortisone, or deoxycortone acetate.

Gastro-intestinal secretions contain rather more potassium than is present in plasma, and loss of these secretions in sufficient amount depletes the body potassium. Even when the total body potassium is not depleted, movement of additional potassium into the cells may lower the plasma potassium. For example, when glycogen is being formed under the influence of insulin the plasma potassium may fall to half its initial value; and in attacks of familial periodic palsy the plasma potassium is low, although there is no net loss of potassium from the body.

Clinical Aspects of Potassium Depletion

Potassium depletion has been recognized in patients with severe diarrhoea or vomiting, during the recovery phase of diabetic coma, and during convalescence from surgical operations. Less common syndromes associated with potassium depletion are Cushing's syndrome, deoxycortone overdosage, familial periodic palsy, and massive saline infusion.

In evaluating the clinical effects of potassium depletion it is important to differentiate between the effects of intracellular and of extracellular potassium deficit. Although the intracellular potassium is more commonly and more extensively depleted than the comparatively small moiety of potassium which is extracellular, the effects attributed to intracellular potassium deficit are somewhat vague. They include apathy, muscular weakness, abdominal distension, and mental disorientation. Such symptoms are obviously difficult to ascribe to any one cause in patients who commonly have depletion of protein and of other electrolytes as well as of potassium, but they have sometimes been found to improve with potassium treatment alone. It should be frankly admitted, however, that the clinical significance of intracellular potassium deficit rests at present more on the proved frequency of such a deficit than on any characteristic syndrome of effects.

No such uncertainty surrounds the effects of extracellular potassium deficit, for a fall in the concentration of plasma potassium is easy to detect and the corresponding clinical syndrome is well defined. Paresis of muscles and generalized weakness are the outstanding clinical effects of lowered extracellular potassium concentration; the paresis may be extensive, and simulate

an ascending Landry's paralysis. The electrocardiogram commonly shows a low flat T wave, prolonged Q–T intervals, and depressed ST segment, the degree of change being dependent on the extent to which plasma potassium is lowered. The low plasma potassium is often associated with a metabolic alkalosis, the plasma bicarbonate being raised; this change may be related to the entry of sodium into the cells to replace a potassium deficit therein.

In the diagnosis of potassium depletion most importance should be attached to a clinical assessment of the possibilities of potassium loss by diarrhoea or vomiting, or by polyuria. A test dose of 10 g. of potassium chloride is normally excreted within 24 hours, and retention of such a dose indicates a potassium deficit of some magnitude. A plasma-potassium level of less than 4 mEq per litre demonstrates depletion of extracellular potassium; but a normal plasma potassium cannot be taken as excluding potassium deficiency, as this may be confined to the cells; moreover, even if the total extracellular potassium is low, this may be masked by loss of extracellular fluid due to concurrent sodium depletion and hence potassium concentration. A rise in the plasma bicarbonate may precede any fall in plasma potassium, since sodium enters the cells at a stage of potassium depletion before the extracellular potassium is involved; but the diagnostic value of this change is lessened by its lack of specificity. Appropriate electrocardiographic changes are useful evidence of potassium depletion, but their absence does not exclude it.

Treatment of Potassium Depletion

An ordinary diet supplies 2–5 g. of potassium daily, and this gives some guide to what must be supplied in treatment. A pint (570 ml.) of milk supplies about a gramme of potassium, and undiluted fruit juices supply a similar amount. Strong coffee has about half this potassium content, and drinks made from meat extracts rather less than coffee. It is therefore possible to give about a normal amount of potassium in a fluid diet, but not to give any great surplus to correct depletion. Potassium chloride can be given in doses of 5 g. at a time without provoking nausea, and the taste can be partly disguised with sweetened milk. About 10–15 g. a day by mouth is a suitable dose for a patient who is recovering from diabetic coma, and should make up the probable deficit in a few days.

When the renal excretory function is normal potassium can be given by mouth without risk, as the amount tolerated orally is well within the excretory powers of normal kidneys. In patients with renal impairment potassium salts should not be given unless the level of plasma potassium can be frequently checked. Oral potassium is the treatment of choice for patients with no gastro-intestinal illness, and intravenous potassium should be limited to those who have a low plasma potassium and who cannot take adequate quantities by mouth.

The risks of giving intravenous potassium are quite definite, and fatal accidents have been reported. The danger lies not so much in the total amount of potassium given as in the speed with which the plasma potassium concentration is increased. The margin of safety is small, as an increase to 10 mEq per litre of plasma potassium produces definite electrocardiographic changes and the risk of cardiac arrest. The concentration of potassium in fluids for intravenous use should not exceed 70 mEq per litre, corresponding to 0.5% potassium chloride, and the rate of giving such a solution should not exceed 4 ml. a minute. Too high a concentration of potassium in plasma causes peaking of the T wave in the E.C.G., cardiac irregularity and arrest, and may also cause paralysis. If any of these signs appear during potassium infusion the potassium should be stopped, a glucose infusion begun, and 5 units of insulin given intravenously. A conservative attitude towards intravenous potassium therapy is justified, and at present it should be limited to patients with actual paresis and a low plasma potassium. Increasing knowledge of the effects of intracellular potassium deficit may broaden the indications for intravenous potassium therapy, but at present it seems best to limit it to patients with an extracellular potassium deficit causing definite clinical symptoms.

LEGAL IMPLICATIONS OF MEDICAL PRACTICE IN U.S.A. AND GREAT BRITAIN

BY

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In considering any legal question regarding the U.S.A. one has to bear constantly in mind the fact that it is not one country, in the British sense of the term, but is in fact the "United States" of America. This aggregate of 48 states is governed by two sets of statute law—the federal law enacted by Congress and applicable to all states, and the state law which is peculiar to, and applicable only in, the state in which it is enacted. While many of the legal aspects of medical practice are fairly uniform throughout the whole country, there are many more which vary from state to state. It would be clearly impossible in one short paper to deal with all the minutiae of variation from state to state, and, in any case, this would be of little interest to British medical readers. It is proposed, therefore, to handle the matter in a general rather than in a detailed fashion.

The Lawful Practice of Medicine

At common law any person who wished could practise medicine. This is precisely the position which existed in Great Britain before the passing of the Medical Act of 1858. In Great Britain any unregistered person may still lawfully practise medicine if he wishes to do so, subject to certain well-known limitations, and provided he uses no title which would lead a member of the public to believe that he is a registered medical practitioner. The American Congress has no power under the Federal Constitution to regulate the practice of medicine. It is a matter over which each individual state has jurisdiction. In all the states medical practice is regulated by statute, and it is provided generally that before undertaking the practice of medicine one must first secure a licence or certificate from a designated body or board.

The practice of medicine by an unlicensed person, or the aiding and abetting of an unlicensed person to practise medicine, constitutes a criminal offence. As in Britain, therefore, the possession of a degree in medicine

does not entitle a person to practise. The procedure in Britain to secure registration and permission to practise, once one has a degree from a recognized institution or examining body, is simple compared with that in the United States. There is no body in America corresponding to our General Medical Council, no direct control over the standards of teaching or examination in individual medical schools, and no system of external examinerships.

However, before a candidate can present himself for certain state examinations he must produce evidence that he has passed the final and qualifying examination for the degree of M.D. (the basic qualification) of an institution approved by the Board of Registration in Medicine. No state will recognize the qualifications of any learned institution. Before a medical graduate may practise he must pass the examination set by the Board of Registration in Medicine for the particular state in which he desires to settle. This would tend to hamper the movement of practitioners from one state to another but for the existence of a certain amount of reciprocity between states. In addition the National Board of Medical Examiners holds examinations, and in all but two states success in this examination will be accepted in lieu of a pass in the state examination. The individual state may provide for the revocation of the right to practise for adequate reasons. The grounds most commonly set forth in the statutes as sufficient to justify revocation of a licence issued to a doctor are: (1) Procuring a criminal abortion even though discharged "not guilty" at a criminal trial; (2) advertising; (3) using an assumed name; (4) giving information about contraception or abortion; (5) aiding an unlicensed person to practise unlawfully; (6) violating the law regarding narcotics or intoxicating liquors; (7) because of gross indecency or immorality; (8) following conviction for a crime—moral turpitude; and (9) unlawful disclosure of a professional secret.

Osteopaths may be licensed to practise in America. To achieve this they must be graduates of schools of osteopathy approved by the American Osteopathic Association and they must pass an examination set by the Board of Registration in Medicine. Once they are licensed, osteopaths may do anything a "legitimate" medical practitioner can do, but they are held responsible in law to the same extent as a medical practitioner and must therefore show a reasonable degree of skill in diagnosis or they would constantly be liable to civil suits. Naturopaths, chiropractors, and the like may be licensed to practise following examination by the appropriate state board. However, by court decision it has been held that, while physicians may prescribe drugs and use a knife, the holders of other qualified certificates may do neither. As in Britain, an unlicensed practitioner may not recover fees in a court of law.

To become a recognized consultant a practitioner in any specialty must fulfil certain requirements as regards postgraduate training and must pass an examination set by the American Board of his specialty.

The Medical Practitioner's Liability in Tort

Every person is liable for his own tortious acts, but, in addition to this, the American doctor may also be responsible for the negligent acts or omissions of others. He is responsible, as his British colleague is, by virtue of the doctrine of "respondeat superior," for the wrongful acts of his agents and unqualified employees done in the course of their employment. In addition to this, however, where doctors practise in partnership, each partner is liable not only for his own acts but also for those of his partner. He would also presumably be responsible for the act of his qualified assistant, even though he took no part in the procedure complained of and would have disapproved of it had he been consulted.

Further, when two or more independent physicians are caring for a patient, each is answerable for his own conduct and for the wrongful acts or omissions of the other or others which he observes and lets go on without objection. Not only may the doctor be liable for the negligence of another than himself, but he may also be liable to a third party—that is, to someone other than the patient and therefore "a stranger to the contract." For example, when he has rendered negligent and harmful service to a married woman, he may be liable to the husband for expenses and loss of services, society, and companionship.

Civil Actions for Malpractice

As in Britain, an American practitioner is required to exercise a reasonable degree of skill and care in the treatment of his patient. If he fails to do this, and the patient suffers injury, the doctor is liable. Also, as in Britain, if a practitioner poses as a specialist and is sued for negligence, he must prove that he possesses those extra attributes which would entitle him to pose as such. Similarly, a doctor's duty to the patient may be terminated at any time by his being discharged by the patient. The physician may also withdraw from the case, but only after reasonable notice has been given to the patient, and when there is reasonable opportunity of filling his place. A physician is not obliged to accept any patient and does not by implication guarantee the results of his treatment.

Actions for malpractice are far more frequent in the United States than in Britain. Some 4,000 such actions were brought against American practitioners in 1937. The intensified competition and economic stress of the last two decades, the breakdown of the traditional patient–doctor relationship, and the increase in "suit-consciousness" due to the large number of personal injury actions partially explain this trend. Where an established doctor–patient relationship exists malpractice suits are rare. It is usually during the first course of treatment that the cause of action arises. There are no professional organizations in the United States devoted exclusively to medical defence. Insurance companies provide cover for doctors to meet contingencies of this sort.

It is in actions of this kind that the so-called "expert witness" makes his appearance. The ordinary witness must, with few exceptions, testify regarding facts. The expert witness may give evidence which is a combination of fact and opinion, or, perhaps, evidence of opinion only. An expert must prove his qualifications to speak as an expert. Generally, in America any licensed practitioner will be found qualified to give expert evidence regardless of the special medical subject-matter under consideration. The fact that the witness has had more or less experience in the special field may affect the weight of his testimony, but apparently not the question of his qualification to function as an expert.

It appears that in America the professional pseudo-expert witness is something of a menace. With reference to this, Regan (1949) writes : "While it is not solely in malpractice actions that highly coloured testimony is given by so-called expert witnesses, it is nevertheless true that in no other field has the 'professional' expert become so prominent or so burdensome. The 'professional' expert witness, the apparently conscienceless physician preying on his colleagues, is, by his profit-seeking efforts, directly and actively contributing to the perversion of justice. It is submitted that he is a menace to the public welfare, and his presence and his activity should be recognized by bench and bar. There is, at present, no effective method of controlling or of punishing him."

The Minnesota plan (Workman, 1947) was developed to try to ensure that medical experts give only fair and honest evidence. This plan contemplates that judges, lawyers, and doctors will be asked to call to the attention of appropriate committees of the medical and bar associations any conscious deviations from the truth that they may observe in the testimony of expert witnesses, and that the transcript of the evidence will be submitted to an impartial group of doctors. Unfortunately, there is no effective machinery by which the culprit may be dealt with. It is suggested that, in a suitable instance, the matter may be reported to the Board of Medical Examiners. It is questionable if, under the provisions of the majority of the Medical Practice Acts, Boards of Medical Examiners have effective authority. In those states where "gross immorality" is defined as unprofessional conduct, it is probable that the Board of Medical Examiners might be upheld if a professional expert witness who consciously deviated from the truth had his licence revoked. The difficulty is in proving that what a person declares is his opinion is not his opinion, but is one given for the special occasion. It really lies with the courts to test the qualifications of the "expert" to speak as such on the subject at issue.

Ordinarily a malpractice action will fail unless some doctor comes into court and gives testimony which, in effect, condemns the defendant physician's conduct in the case. The plaintiff's expert may generally be relied upon to express the opinion that the defendant's conduct of the case was not consistent with the standard of practice in the locality, that the defendant did something which the ordinary reputable doctor would not have done, or omitted to do something which the ordinary reputable practitioner would have done, and, as a result, the injury occurred.

Negligence on the part of a doctor will not be presumed ; it must be affirmatively proved. In the absence of expert testimony when the doctrine of "res ipsa loquitur" is not applicable, it will be presumed that the doctor exercised the ordinary care and skill required of him in treating his patient. The plaintiff must show not only that the physician failed to fulfil the legal duty owed to the patient but that, as the result thereof, the injury complained of proximately occurred. A physician is not liable for an honest error of judgment.

In some cases medical expert testimony is not necessary. This is so when the doctrine of "res ipsa loquitur" is held to apply. The inference of negligence on the part of the defendant, to which the application of the doctrine gives rise, is sufficient to take the case to the jury and to sustain a verdict and judgment for the plaintiff. The doctrine of "res ipsa loquitur" applies to cases of slipping instruments ; foreign bodies left in the tissues ; burns from hot-water bottles, compresses, lights, etc. ; x-radiation injuries ; infection through the use of an unsterilized instrument ; and injury to a portion of an anaesthetized patient's body outside the field of treatment or operation. This latter aspect of American medical law is quite different from the British. Here, the doctrine of "res ipsa loquitur" does not apply in such cases. Each case must be judged on its own merits, and, if it is proved that in spite of all reasonable precautions the accident happened, then the practitioner will not be judged negligent. In Britain the courts are reluctant to find against a practitioner unless he really has been negligent in some regard.

Coroners and Medical Examiners

The provisions for dealing with sudden, suspicious, unexplained, or violent deaths vary greatly from state to state. In most states the office of coroner exists. The coroner is an official voted to office on the basis of a popular political vote. He may happen to be a medical man, but might be a tradesman with no knowledge of law or of medicine, and in many less-developed areas the local undertaker is also the coroner. In a few states the coroner must be a medical man. The right to order a necropsy is incident to the coroner's duty, and the coroner may, in his discretion, employ a pathologist to conduct the post-mortem examination. Because election to office is on a temporary basis, and is subject to political favour, it can readily be seen that such an arrangement might become corrupt. In a few jurisdictions the office of coroner has been abolished (Massachusetts, New Hampshire, and New York City) and medical examiners have been appointed instead. In a number of others (Connecticut, New Jersey, and Rhode Island) both the office of coroner and that of medical examiner are in existence.

Where a medical examiner has been appointed all unexplained, suspicious, or violent deaths must be reported to him and he is required to investigate them. If a coroner holds office the medical examiner reports to him those cases which require a public judicial inquiry. If there is no coroner the medical examiner reports such cases to the District Attorney (Public Prosecutor), and an official public inquiry or inquest is held before a judge of the District Court. Where there is a medical examiner he has full authority to make post-mortem examinations when he deems it "in the public interest," and to collect such information as he may require for purposes of his investigation.

Medical examiners do not have absolute power to perform a necropsy as coroners in Britain have to order one. It is felt that before he can do so there must be some suspicion of unnatural death. He must be in a position to justify a necropsy should the relatives object and later bring suit against him for performing one without consent. Because of this the medical examiners rarely make post-mortem dissections in those cases in which there is some sort of medical history on which a diagnosis could be made and no evidence, on external examination of the body, to support the thesis of violence. In jurisdictions having medical-examiner systems, a necropsy is performed in approximately 10% of the cases reported. The medical examiner must furnish a certificate giving the cause of death, the manner of death,

and whether accidental, suicidal, homicidal, or natural. He thus has to return a verdict on the case much as a coroner in Britain has to do, but he cannot hold an inquest. In large cities the medical examiner is a medico-legal specialist usually in charge of a university department. In small towns he is a local practitioner, who may deal with a case on his own authority, but who usually calls on a pathologist when a necropsy becomes necessary.

Sterilization

Eugenic sterilization laws are on the statute books of 29 of the states. There is no comparable legislation in Great Britain. In general, these laws provide for the sterilization of persons suffering from certain hereditary mental diseases and deficiencies who have been committed to hospitals for the insane. In most states sterilization of a private patient is a crime unless justified by medical necessity.

Artificial Insemination

In the United States artificial insemination, so far as its practice with human beings is concerned, apparently has no established legal status. There is no legislation on the subject. There is a presumption in law, which is widely accepted, that a child born in wedlock is legitimate. With its unestablished legal status, even if not contrary to law, the practice of artificial insemination, using a donor other than the husband, is hazardous to the doctor who performs it. The position in both countries, therefore, is uncertain, as there is almost complete lack of authority either by statute or by judicial decision. There seems to be a need in both countries for legislation on this subject.

Professional Secrecy

The principles of the Hippocratic oath apply to the obligations of American doctors. However, in the United States, in contrast to Great Britain, therapeutic privilege is not allowed, and if a patient is seriously ill and likely to die there is a duty on the doctor to tell him so.

As is generally known, a doctor in Great Britain may be ordered by a court to divulge information obtained from the patient by reason of their professional relations, and should he refuse to do so in defiance of the court he may be held to have committed contempt of court. In most jurisdictions in America, communications between a doctor and his patient, arising from the professional contact, are deemed of such a confidential nature that the courts do not demand disclosure even in the interests of justice, and statutes have been enacted excluding them as evidence, on objection. Further, hospital records are treated in the same way. However, where a person is examined by a doctor at the instance of the police, and the patient does not object when the purpose of the examination is explained to him, he cannot thereafter object to the doctor's divulging his findings in court. If a patient is suffering from a contagious disease the doctor may disclose to others the patient's condition if the latter refuses to do what is necessary in the interests of public health. Such a situation would be covered by qualified privilege in English law.

Criminal Responsibility

In general the M'Naghten rules of English law are the basis for determining criminal responsibility in all the states and in federal courts. In Britain irresistible impulse is not accepted as a defence, but in 12 American states it is. If a person indicted for murder or manslaughter is acquitted by the jury by reason of insanity, he is committed to a state institution for life, or till the Governor of the state and his council are satisfied that his discharge will not cause danger to others.

Commitment of the Insane

For the most part the certification of the insane is left to the psychiatrist in the United States. In correspondence to the British "reception order on petition," a person may be committed to an institution for the insane by a judge of the Superior Court, or of a District Court of a county. The petition must be supported by two medical certificates, one of the signatories must be a consultant psychiatrist, and the judge may, if he considers additional medical evidence desirable, appoint a third psychiatrist to examine and report. No staff member of the institution to which the patient is to be committed may sign one of the certificates. As an alternative to final commitment, the judge may commit the patient for observation for a period of 40 days, pending determination of his mental condition. Two medical certificates as above are required. Within 30 days the superintendent of the institution must discharge the patient, if found sane, and notify the judge, or, if found insane, report to the judge recommending committal or discharge under guardianship. Temporary care of persons violently insane may be effected without court order on certificate from two doctors qualified as above, by the superintendent of any institution for the insane. This is effective for five days. Temporary care of insane persons requiring immediate attention may be arranged on the request of a doctor, sheriff, or police officer. This is effective for ten days.

Dangerous Drugs and Narcotics

The drugs of addiction whose distribution is covered by the law are roughly the same in both countries. The laws governing this matter in the United States are part federal and part state. Under the Harrison Narcotic Law a doctor wishing to administer or dispense narcotics must apply to the local Collector of Inland Revenue and pay a tax of $1.00. In return he receives a special tax stamp, which includes a Narcotic Registration Number assigned to the doctor and to his premises. Stock narcotics for emergency use or dispensing are obtained by ordering on an official Government order form from wholesalers or manufacturers, not from retail pharmaceutical chemists. A duplicate copy must be retained by the doctor for two years, and a daily record of the kind and quantity of narcotic dispensed, and the name and address of the recipient, are required.

The regulations governing the writing of prescriptions for narcotics is substantially the same in both countries.

In addition to all this, in the United States there is a large group of substances which can only be "dispensed by or upon the prescription of a physician." The term "dangerous drugs" is applied to these, not as in Britain to drugs of addiction. Under the current federal interpretation of the law a pharmacist cannot redispense a prescription for any of these preparations unless the doctor clearly indicates that he desires this to be done, the number of times it may be done, and/or the period of time within which it is permissible.

Registration of Births and Deaths

In Britain a medical practitioner has no responsibility regarding the registration of births; in the United States he has. A doctor is required to make a report to the clerk of the city in which the birth occurred, within 15 days of every birth of which he has been in charge. Illegitimates retain the mother's surname, and the facts concerning the father are not returnable except on written consent of both parents.

There is no certificate of stillbirth in the United States. In all cases of stillbirth the doctor must return a certificate of birth and one of death. Such certificates must be completed if a child is born dead after 20 weeks of intrauterine life. In some states premature births must be notified to the Board of Health (Public Health Department) in order that special provision may be made for care of the infants. Deaths may be certified in three ways. The practitioner in attendance may certify if he knows the cause of death and was in attendance during the last illness. If a person has been disabled by recognized disease unrelated to any form of injury and dies without medical attention, then death may be certified by a Board of Health physician. Often such cases are reported to the medical examiner, and, if the cause of death is reasonably certain and there are no suspicious circumstances, he may decline jurisdiction and leave the Board of Health to certify the death. The third method is where the medical examiner certifies the cause and manner of death as detailed above.

Reporting of Gunshot Wounds

In a community where so many members possess firearms, and are accustomed to their use, it is not surprising that the incidence of fatal shooting is high. By law, therefore, every physician attending or treating a case of bullet wound, gunshot wound, powder burn, or any other injury arising from or caused by the discharge of a firearm shall report the case to the police and to the commissioner of public safety. The purpose of this law is not only to prevent concealment of homicidal attack but also to expedite police investigation in cases of stray bullets, and to eliminate the public hazard of weapons in incompetent hands. No corresponding duty falls on the British medical practitioner.

The material for this paper was accumulated while I was a Research Fellow in Legal Medicine at Harvard University Medical School, Boston, Mass., U.S.A., and in receipt of a Smith-Mundt grant from the United States Government. I wish to express my gratitude to the State Department for making this period of study possible and to the staff of the Department of Legal Medicine at Harvard University for their courtesy and kindness.

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According to reports in the *New York Times* (November 9) attempts are being made both in Japan and in Washington to isolate the organism causing the virulent haemorrhagic fever recently contracted by troops in Korea. 25 deaths have been attributed to the fever, sometimes known as Koka disease or Korin fever, states the Surgeon General, and a total of 196 cases has been reported. The fever was first recognized by the Japanese Army in 1939, and it first appeared among United Nations troops in June this year.

Nova et Vetera

ABRAHAM VATER (1684–1751)

Though the name of Abraham Vater is familiar to every student of anatomy and to every surgeon, on the occasion of the second centenary of his death, which falls on November 18, Sir Thomas Browne's words have a peculiarly sober ring: "To be content that times to come should only know there was such a man, not caring whether they knew more of him." One of the most versatile men in the annals of medicine, Abraham Vater, son of a distinguished German doctor, was born in Wittenberg on December 9, 1684. After taking a doctorate in philosophy from his native university in 1706 and a doctorate in medicine at Leipzig four years later, he travelled in Germany, England, and Holland. In 1719 he was appointed professor of anatomy and botany at the University of Wittenberg, and in 1737 was elected to the chair of pathology and therapeutics. Known to-day chiefly as an anatomist, Vater, though he specialized in that subject, sacrificed nothing thereby to the breadth of outlook of the scientist, writing extensively on surgery, gynaecology, pharmacology, pathology, therapeutics, chemistry, and botany. He is eponymously commemorated in the ampulla of the common bile-duct, which he described in 1720 in his *Dissertatio anatomica qua novum bilis diverticulum circa orificium ductus choledochi . . . .*, and in the corpuscles of Pacini-Vater *(Oeconomia sensuum ex speciali organorum sensoriorum et sigillatim ex papillarum nervearum textura mechanice demonstrata, 1717).* His other contributions to anatomy include research on the mechanism of the closure of the foramen ovale and a section in the *Opera omnia anatomico-medico-chirurgica* by Fredericus Ruysch, his former teacher in Amsterdam.

Preparations and Appliances

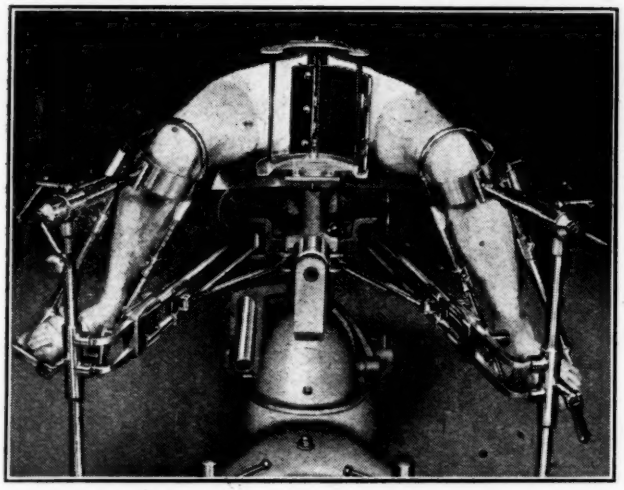
NEW OPERATING-TABLE FITTINGS FOR OPERATIONS ON FRACTURES OF NECK OF FEMUR

Mr. A. N. BIRKETT, F.R.C.S., orthopaedic and accident surgeon, Nottingham, writes: Operation on fractures at the hip has now become a standard procedure in most traumatic centres throughout the world. Insertion of Smith-Petersen pins for fracture of the surgical neck of the femur and the insertion of various forms of pin-plate for basal or intertrochanteric fractures are straightforward surgical procedures, provided satisfactory apparatus is at hand. Efficient mechanical fixation of the patient and injured limb must be maintained; free surgical access must be possible; and rapid facilities for *x*-ray examination, in a manner that does not impede the surgeon, must be available.

About 11 years ago I had made, at the Nottingham General Hospital, a special pelvic rest and special leg irons which gave satisfactory service until the end of the war. More recently I have had the original apparatus replaced by one made to fit a modern operating-table. The pelvic rest, made of metal and plastic, allows the introduction of a curved cassette between the legs so that a lateral view of a fractured neck of the femur can be readily taken and repeated, the cassette being fixed so that it can be handled by non-sterile personnel in the theatre. The antero-posterior film cassette can also be introduced without interference with sterile towels. When using this pelvic rest no difficulty is found in taking quickly both antero-posterior and lateral views with one *x*-ray machine.

The fixation of the patient on the table is arranged with leg pieces holding the lower limbs with the knees in flexion.

By this means traction on the limb is carried out with an adjustable sling behind the calf, and flexion of the knees is maintained by a strap over the instep, the foot being placed on an adjustable foot-plate. The traction bar lying along the axis of the femur can be turned to allow rotating movement of the hip, and the position be fixed so that the femoral neck can be brought into approximately the horizontal position. The degree to which the leg is rotated can easily be checked on the lateral *x*-ray film by observing whether the neck of the femur lies squarely on the film or whether it is lying obliquely. Traction, rotation, and abduction are all easily adjustable during the operation. Curved intersecting rails allow the curved cassette to be introduced blindly and locked into position by a simple locking device. The leg-rest is adjustable to the stature of the patient.



The illustration shows the symmetrical position of the legs on the table. Standing between the legs, palpating both hip-joints at once, it is easy to feel whether the attempted reduction has produced symmetry of bony points or not.

I have used this type of apparatus for some 11 years, and can thoroughly commend it for routine pinning and pin-plating. The apparatus has been made by the Medical Supply Association, and constitutes a valuable addition to the equipment of their already comprehensive Plaistow combined orthopaedic and general operating-table. The apparatus is designed to take curved cassettes made by Messrs. Kodak, dimensions 8½ in. by 6½ in. (21.6 by 16.5 cm.).

In his *Annual Report for 1950* the medical officer of health for Poole points out that little attention has been paid to the bacterial purity of the sea water on the bathing beaches around our shores. Recent tests have shown that there is gross sewage pollution of the waters of Poole Bay, the sands of which extend for 10 miles and provide the bathing beaches for Christchurch, Bournemouth, and Poole. Nine outfall sewers discharge into Pooie Bay the sewage of a population of a quarter of a million people, untreated except for disintegration and a modicum of chlorination. There is more pollution of the sea than there is of the enclosed water of Poole Harbour, despite the large built-up area on its eastern shore. Elsewhere in his report Dr. Chesney states that the immunization against diphtheria of the child population of the borough has been assiduously practised since 1929. In 1935 he first reported that in his experience the most effective method of immunization was by two widely spaced doses of alum-precipitated toxoid, a method which has since become the most widely used in the world. During the past year there was not a single case of diphtheria in the borough, which has a population of 82,140.

Reports of Societies

TREATMENT OF MAXILLARY SINUSITIS

On November 2, at a meeting of the Section of Laryngology of the Royal Society of Medicine, Mr. A. M. Zamora invested Mr. F. C. W. CAPPS with the jewel of office and called upon him to read his presidential address, "Observations on the Treatment of Infections of the Maxillary Antrum."

After a brief review of the history of the subject, Mr. Capps said that, except for casual cases attending as out-patients or occurring during their stay in hospital, the rhinologist was not often called upon to treat maxillary sinusitis in the very early stage, when medicinal methods were most appropriate. This was the province of the family practitioner, who should insist upon a proper period in bed to prevent the spread of infection. If this could not be done at home, Mr. Capps suggested that patients should be admitted to the medical wards of hospitals and be under the care of a physician, and he deplored the withdrawal of general-practitioner beds which had occurred in the last few years.

He then surveyed some 200 cases which he had treated in his private practice; two-thirds of these patients were between the ages of 20 and 60. Of cases coming for consultation in the subacute or chronic stage, which might be established very early in the disease, a very large proportion were cured by a single lavage and conservative treatment, only 5 of 61 such cases being failures. When surgical drainage was required the adequacy of intranasal antrostomy appeared to be well established; 82 of 93 such operations had given outright and lasting cures, and the commonest cause of failure was closure of the opening. More radical procedures, such as the Caldwell-Luc operation, were reserved for something less than 10% of the total, and the chief causes of failure there were polyposis, dental sepsis, and ethmoiditis. He reviewed a group of "dental" cases, and also a group of cases of bilateral disease, in which intranasal surgery was done on one side and radical sublabial surgery on the other.

Conservative Treatment

Treatment of the acute stage and its complications had been revolutionized by chemotherapy and antibiotics. Protection was thus provided against the consequences of injudicious or over-zealous nasal surgery, though the aftermath in some was still liable to be deplorable. "A comfortable nose is a very desirable thing." Mr. Capps was doubtful of the benefit of penicillin locally in the mouth or in the antrum, but advised 300,000 units of "distaquaine-G" twice a day parenterally. It seemed a mistake to rush off to the newer antibiotics just when they had begun to learn how to use penicillin and what it could do. He particularly advised a lavage at the end of the course of treatment. Children should be isolated in special clinics and their antra should be punctured only under general anaesthesia and in hospital. Polythene tubing seemed advantageous. In the surgery of the antrum, as in many other fields, "conservatism indicates progress."

Details of Surgical Technique

In the discussion which followed, Mr. A. WALFORD strongly advocated an indwelling catheter for three, five, or seven days for repeated washouts as preferable to an intranasal antrostomy, which all too often meant constant reinfection.

Mr. J. C. HOGG made a plea for local anaesthesia in making the intranasal opening. Performed like this it was

a relatively minor operation, and could even be carried out in the consulting-room. He had found polythene tubing particularly suitable for children, and perfused with isotonic saline solution, rather than solutions of penicillin, twice a day. In very elderly people, who were often edentulous, he recommended alveolar drainage if they were not fit for more radical surgery. A plug was fitted to the denture; they swilled the mouth out once a day with a lotion, some of which returns through the nose; "and they worry the doctor no more."

Professor F. C. ORMEROD advised that puncture of the antrum should be delayed, and mentioned the plugging of the nose with hydrogen peroxide, mild silver proteinate ("argyrol"), and "collosol iodine." When he added that penicillin was useless inside the antrum several members rose, and it was soon clear that the majority opinion was against him. Mr. C. GILL CAREY favoured a general anaesthetic for puncture of the antrum. Mr. GAVIN YOUNG, Mr. W. A. MILL, Mr. WATSON, and others discussed the indications for intranasal antrostomy and the Caldwell-Luc operation with their various advantages and disadvantages. Mr. C. HORSFORD remarked that the prognosis in many cases probably depended upon whether the natural ostium was normal in size or very small. Mr. C. HAMBLEN-THOMAS doubted the value of some *x*-ray reports which stated that the antra were normal. He advocated replacement therapy and, in children, more co-operation between rhinologist, general practitioner, and paediatrician, directed towards the patient's general health.

Treatment of the Early Stages

Mr. CAPPS replied briefly, but, stimulated thereto by a general practitioner in the back row, he outlined his immediate treatment of an infection of the antrum in its very early stage. The patient should be in bed. To stay at home half the day and then go to the office was asking for trouble, as the nose was extremely sensitive to changes of temperature. Even to walk from a warm bedroom along a cold passage was liable to produce acute congestion of the nasal mucous membrane. Heat applied locally—by hot water-bottle, for example—and the inhalation of medicated steam were helpful, as was also the insufflation or dropping of 0.5% ephedrine in normal saline into the nose. In the absence of severe toxaemia he would not resort to penicillin at once, as so many infections responded without it; but sinusitis was a debilitating process, and recurrence after recovery was all too probable, unless a period of convalescence, preferably with change of air, was enforced.

In a paper in the *Biochemical Journal* (1951, **49**, 199) A. Neuberger and his collaborators at the National Institute for Medical Research at Mill Hill report that the protein of the collagen of white tendons is very inert metabolically, in the rat at least. When a radioactive amino-acid such as glycine is fed to an animal it is very quickly built into some tissues such as the liver, less quickly into others such as muscle, and only extremely slowly into tendon. Further, when the animal is put back on a normal diet the radioactive glycine is eliminated from the proteins of the tissues, very quickly from liver, more slowly from muscle, and little or not at all from tendon, and these changes are independent of growth, since they are found in fully grown adult animals. The interpretation is that some tissues are metabolically active, that their structure, though seemingly stable and finished, is constantly being broken down and re-formed on a submicroscopic or molecular scale. One result of this is that many tissues and organs retain their adaptability even when fully grown. However, it seems that tendon is not among this group but is only slowly constructed by the body, and once built stays put, as if already dead.

Correspondence

Exercises in the Bath

SIR,—For treatment of tuberculosis of the lungs I suggest that the exercises in the bath designed by Mr. T. R. Togna (*Exercises in the Bath*, Caxton Press, 1950) would be excellent to follow rest in bed and before exercises in air are taken. The exercises would greatly relieve the mental strain of lying in bed and lighten the nursing work of washing the patients, and if carried out with moderation need increase the volume of air breathed only slightly while keeping pulse rate and blood pressure almost unchanged, and yet adding greatly to the use of oxygen by the tissues.

In exercises in air we are confronted by the cost of supporting and imparting motion to body weight. This cost is reduced from 10 stone to 10 lb. by the buoyancy of the water in a bath. The energy thus saved can be used in performing the exercises in the bath, an activity which calls into a concerted muscular action all parts of the body with uniformity. The mechanical work done permits the skeleton muscles to extend fully. By so doing the flexibility of the muscular tissue of the whole body and its circulatory system are well maintained. Contributory advantages to economize the cost of the action are recumbent posture and the support of the walls of the bath. Water resistance, which increases the cost of swimming, is avoided.

Tests made on various subjects by 10 minutes' exercise in the bath prove that with a decrease, or an increase, of only a few beats in pulse rate the oxygen absorption doubles or trebles that of the basal state, while the blood pressure is not raised. And, so far as it was ascertained two hours after the activity, an increase in oxygen intake was maintained. In seven subjects the volume of air breathed per minute was increased individually from 6,040 to 12,700; 6,930 to 14,750; 5,790 to 13,900; 7,470 to 18,000; 12,500 to 14,250; 8,400 to 9,500 ml.; small increases compared with those during exercise in air. By moderating the exercises the increase can be kept low, as it is in the last subject.

In active muscles not only are more capillaries open but their average diameter is greater than in resting muscles. The number of capillaries in a square millimetre of muscle may be enormous, often above 4,000. As they open up they may increase the volume of blood in the muscle to a surprising degree. Krogh calculated that the volume of blood in active muscles of the guinea-pig may be 275 times as large as in resting muscles; while if all the capillaries were fully opened it would be 750 times as large.

Together with this effect on the muscles compared with rest in bed, exercises in the bath will afford adequate circulation to supply oxygen and remove waste substances from the nervous system and so increase the morale of the patient. Further, they will afford a better circulation of the endocrine glands and keep these in adequate touch with the living processes.

Mr. Togna had several of his family die of tuberculosis and himself suffered five attacks of pneumonia between 16 and 27 years of age, followed in one instance by phlebitis of the left leg. He also had haemoptysis and bronchial catarrh, and for 20 years endured a catarrhal condition of the nose and throat, indigestion, and haemorrhoids. Rejected for life insurance at the age of 48, he found relief when at 52 years of age he started the exercises in the bath. The evidence of his present fitness, exceptional muscular flexibility, and power of recuperation after strenuous activity shows an extension of fit middle age, and he has relieved himself of all minor rheumatic troubles by these exercises. Now, at the age of 77, Mr. Togna can easily run 81 yards in 12 seconds, and has been passed as remarkably fit in every way by his medical examiners. He is a most encouraging example of what can be done for tuberculous patients by a method designed to exercise and bring oxygen to all parts of the body with little expenditure of energy and no fatigue, but rather exhilaration, and a good preparation for sleep.—I am, etc.,

Lowestoft. LEONARD HILL.

"Primary Atypical Pneumonia"

SIR,—May I congratulate Squadron Leader Philip W. Robertson and Dr. K. D. Forgan Morle on their paper (October 27, p. 994), which goes far in clarifying the confusion concerning the conditions of "pneumonitis" and "primary atypical pneumonia"? As a general practitioner I have been impressed by the incidence of acute pulmonary infections which present a clinical picture similar to that described in their paper. Over the past four years I have seen some 50 patients with this condition. Of these there was a male preponderance, and their ages varied from 3 to 80 years, the majority coming in the 5–30 years group.

The clinical features were characteristic. There was an insidious onset, following an upper respiratory tract infection, which instead of settling down was complicated by a very irritating and distressing cough. This became productive in a few days, the sputum often being blood-stained. The general condition was remarkably good. There was never fever above 101° F. (38.3° C.) and the pulse rate did not rise over 95. In no case was there any respiratory distress. The chest signs consisted of a localized area with impaired percussion note, diminished air entry, and inspiratory rales or crepitations. This area was, in the vast majority, at one or other lung base. There were only two exceptions; in one patient the signs were at the right upper zone and in the other the left mid-zone was affected.

Unfortunately it was not practicable to carry out a routine chest *x* ray in most of the patients, who were all treated in their homes. It was possible, however, to arrange a chest *x* ray while the signs were still present in 10 cases. In four patients an area of collapse corresponding to the clinical signs was noted, shadows reported as "patches of pneumonitis" were seen in four others, and in two cases no abnormality was detected in spite of the clinical signs present. Sputum analyses merely revealed organisms which are normal inhabitants of the upper respiratory tract. The chest signs cleared completely in 10 to 21 days, and no patient was hospitalized.

I treated these cases with a variety of antibiotics—i.e., sulphonamides, penicillin, chloramphenicol, and aureomycin. It is my impression that these drugs did not really influence the time taken for the signs to clear. There was, however a marked improvement in the patient's general condition within 48 hours of giving either penicillin, chloramphenicol, or aureomycin. It is reasonable to suppose from this observation that these drugs rapidly controlled the inflammatory condition of the lung but that the re-expansion of the affected collapsed area took a much longer period.

Even prior to reading Sqn. Ldr. Robertson and Dr. Morle's paper I felt that these cases were examples of a mild form of aspiration pneumonia, this statement being supported by the history, signs, radiological findings, and by this response to antibiotics. Since reading their paper I feel all the more convinced of this aetiology.

There are two points, however, which I, personally, cannot explain adequately. Why is this condition most common in the young age groups? Why are the bases most often affected? It may be interesting to comment that during this same period of four years only two cases of classical lobar pneumonia were seen. This condition seems to be becoming rare, at least in my practice. I hope to present for publication a fuller report of these cases at a later date.—I am, etc.,

Beckenham, Kent. JOHN FRY.

SIR,—The article by Squadron Leader Philip W. Robertson and Dr. K. D. Forgan Morle (October 27, p. 994) raises a number of interesting issues.

The authors present evidence to prove that the condition is produced by the inhalation of material from the upper respiratory tract, and seem to suggest that the occurrence of this symptom is quite independent of bacterial or virus infection. They suggest that all their cases followed upper respiratory infection, but at the same time discard the notion that such infection caused the pneumonitis. It has been known for some years that upper respiratory infection can produce symptomless shadows on routine *x*-ray examination of the lungs. This, too, has been recognized as an inhalation phenomenon, but in the absence of symptoms and physical signs surely the diagnosis of pneumonia, "atypical" or otherwise, is hardly justified.

So far the arguments brought forward simply confirm the recognized view that the bronchiole is still the high road to the alveolus. It is suggested that the condition is unlikely to be due to a pneumotropic virus. It may be some consolation to think of the virus as being either rhinotropic or pharyngotropic, but nevertheless it must be a pathogenic virus if by definition it follows the rules of virus propagation and produces clinical and radiological features of pneumonitis. It has not been suggested that the virus itself produces segmental collapse; the mucoid medium in which it is carried obviously does this. Nor does the virus roam of its own free will, but is passively borne in its mucoid menstruum under the control of other forces, of which gravity is one and ciliary action another.

We still remain with the conclusion that "primary atypical pneumonia" is a heterogeneous collection of infective conditions, some being obviously due to aspiration of infective material from established upper respiratory infection, some arising primarily as pneumonitis without such infection having been present in the upper respiratory tract.

In a small series of 51 cases which I had the opportunity of studying some years ago, only 14 commenced with symptoms of respiratory or generalized infection. These symptoms consisted of coryza with general malaise and headache and lasted for a mean period of four days. In this series also I was able to demonstrate a triad of migrating pneumonitis, patchy atelectatic areas on *x*-ray examination, and an unusually high incidence (about 75%) of positive cold agglutinins in the serum (*Lancet*, 1947, **1**, 865). The infectivity of this particular type of infection was observed through four cases, incubation period for the second, third, and fourth cases being three weeks, all but the first (who was not tested) producing high titres of cold agglutinins. Finally, culture of the sputum produced two different pathogenic organisms in two of these cases. The severity of the clinical courses of these cases differed markedly in association with the difference in pathogenicity of the two organisms concerned.—I am, etc.,

Birmingham. G. E. OWEN WILLIAMS.

Bornholm Disease

SIR,—As a result of my interest having been drawn to Bornholm disease by the recently reported epidemic in Oxford, I believe that I have been seeing quite a number of cases. From these cases I consider the following points worthy of note.

There is frequently a short prodromal period of general malaise and headache before the dramatic onset of the outstanding feature of pain.

In cases simulating pleurisy close questioning will elicit that the pain is described as more of a colicky nature than the sharp stab of a knife.

Wherever the site of pain, it is aggravated by movement of the body.

Vomiting is uncommon; however, in one case of pleural-like pain the patient could retain neither solid nor fluid for the first 24 hours. My assumption is that the swallowing reflex irritated the infected diaphragm, causing spasm of the cardiac orifice of the stomach and immediate reverse peristalsis.

—I am, etc.,

Westcliff-on-Sea. B. S. QUINN.

SIR,—The article by Drs. J. B. M. Davies and J. F. Warin (October 20, p. 948) and subsequent correspondence have prompted us to describe a series of cases which we have seen during the past six weeks, and which we thought to be similar to the epidemic pleurodynia described in the *Journal* of 1950. We have seen six severe cases and nine mild ones.

The patients with severe attacks have all been adults, and have described an illness of acute onset with headaches, malaise, and generalized aches. All of them have complained bitterly of a severe pain, either subcostal or related to the lower ribs. The pain is not accompanied by a cough, nor is it affected by deep breathing. Most of these patients have had nausea, and a few have vomited repeatedly.

The temperature has varied between 100° and 104° F. (37.8–40° C.) at its maximum. It has tended to swing, some cases being remittent and others intermittent. The lowering of the

temperature has been accompanied by a drenching sweat, during which the patients have felt exhausted and anxious, and two have said they thought they were going to die; these sweating episodes have occurred once or twice during the 24 hours.

The patients have had an ill and anxious look, but in the early stages we have found no abnormal physical signs. After four or five days of this pyrexial illness we have heard a definite rub over the lower ribs on one or both sides of all the severe cases. In two cases the patients have heard their own rubs, and in one case it was so loud that it was heard by the wife, who had not the advantage of using a stethoscope. In no case have there been signs of lung involvement, and in none have we found any signs of meningeal infection. The severe type of case appears to run a fever for ten days, at the end of which time the temperature falls and the patient is left very weak, and gradually recovers strength in a further ten days. There has been a loss of weight of up to a stone. We have noticed that the pleural rub will continue for up to a week after the temperature has fallen. The mild cases have included two adults and seven schoolchildren. The general picture has been the same as in the severe cases, but they have run a milder and shorter course. The occurrence of some of them in the same house as the severe ones makes us certain that we are dealing with cases of the same condition. A study of cases occurring in contacts leads us to suppose that three to five days is the usual incubation period.

We have had white cell counts on two patients; the first had a normal differential count, the second had a marked leucopenia which had returned to normal 14 days later. Chest *x*-ray pictures were taken on one patient when the rub was still loud, but no abnormality was seen in the lung fields.

As regards treatment, we have found that tab. codeine co. or mist. sod. sal. will relieve symptoms, but do not affect the course of the illness. Sulphonamides have no effect whatsoever. Two cases were so ill that it was decided to try chloramphenicol 4 g. in divided doses during the 24 hours. There was a prompt and dramatic response. The temperature fell, and the erstwhile ill and apprehensive patients expressed a feeling of well-being within 12 hours and were sure that they would recover.

We feel that this illness is due to a virus infection which, though generalized, has a predilection for the muscles of the diaphragm. The similarity of this outbreak to others already described under the terms Bornholm disease, epidemic pleurodynia, and so on suggests that there is a group of viruses responsible for these related conditions, and that they are much more common than is generally supposed.—We are, etc.,

G. SWIFT.
Winchester. F. C. HEATLEY.

Blood Tests for Bornholm Disease

SIR,—Might I be allowed to suggest that increased facilities for blood agglutination examinations are desirable for practitioners dealing with illnesses due to the Bornholm-Coxsackie group of viruses? Personally, I find diagnosis on purely clinical grounds often difficult for the following reasons:

Differentiation between Bornholm disease and primary atypical pneumonia is not easy in the absence of radiological examination, as some cases of Bornholm disease have a coincidental preceding upper respiratory tract infection.

Some cases have marked headache and some neck stiffness without the preceding abdominal pain, and one has to visit such cases at frequent intervals to make sure they are not cases of meningitis.

Although one can distinguish typical cases of influenza easily, one sees many cases of short febrile illness which, in the absence of more definite information, one has to label "two-day flu."

As reported at the second International Poliomyelitis Conference (*Journal*, September 22, p. 731), in an epidemic of poliomyelitis many cases of Bornholm disease may be labelled abortive poliomyelitis.

Although one type of sore throat, herpangina, has been attributed to the Bornholm virus, one saw during the epidemic many cases of sore throat with pyrexia, the only physical signs being congestion of the pharynx and the soft palate. These cases subsided without one ever knowing their aetiology.

I fully realize that any increase in laboratory work is undesirable, but I feel it is impossible satisfactorily to study the epidemiology of a disease if in many cases the diagnosis cannot be made with certainty.—I am, etc.,

Chipping Norton, Oxon. F. E. JAMES.

More Blasts on the Trumpet

SIR,—At last there is a breath of fresh air in Mr. W. Grant Waugh's letter (November 3, p. 1088) and your leading article (p. 1074). Sanity in the presentation of statistics has been long awaited by most of us who have to read papers. One supposes sometimes that some graphs may have duality of purpose, in the first place acting as an intelligence test; if one can attain "genius grade" in the test, one may then be able to glean some scientific information. My personal feeling is that such graphs could hardly be more unintelligible if they were written in Sanskrit.

I would like to add another plea that the summaries of articles in the *British Medical Journal* be improved, to the extent that they are made self-contained and to incorporate the main facts in round figures which can be more or less easily memorized. Too often the summary is useless without wading through the whole article. One may be interested in reading one's own subject *in detail*, but potential interest in other spheres is killed if one has to negotiate a mountain of minutiae in a limited time, and the tendency is to turn to a more readable article. This is unfortunate. Though I was nurtured in the modern regime of specialization, my belief is that nearly every doctor can do better for one or two more of his patients every year if he is able to get an up-to-date knowledge of development in technique and treatments in other spheres. But perhaps the present trend in article writing is to discourage one from delving into matters outside one's own subject.—I am, etc.,

Chertsey, Surrey. JOHN N. BADHAM.

SIR,—I am interested in Dr. W. Grant Waugh's letter (November 3, p. 1088). I am in thorough agreement with him. Once again it has been shown that medicine is not a matter of mathematics and exact science.

Take, for instance, the tests that have been carried out—pseudo-scientific tests in my opinion—concerning the effects of alcohol on car driving. I agree that a moderate quantity of alcohol will increase a man's reaction time, but that is not the only factor. To use a cliché, "circumstances alter cases." I would rather be driven by a steady middle-aged man who has had a drink, but sober, than a reckless young man who thinks of nothing but speed, but who has had nothing to drink. Yet teetotal societies use the evidence of increased reaction time to put forward their views. I think that a man who drinks, no matter how little, before driving a car deserves all he may get, but that is another question.

Then again, take the form which I have received this last week, asking for information regarding my smoking habits. Will all the figures obtained, and compared with the returns of deaths from lung carcinoma, ever prove anything? One could multiply these examples *ad infinitum*.—I am, etc.,

Liverpool. T. O. WILLIAMS.

SIR,—The letter of Mr. W. Grant Waugh (November 3, p. 1088) is timely. But we who are graduates have our remedy—we can always pass on to the next article or paper, or consign the whole issue to the waste-paper basket. I write rather on behalf of a defenceless section of our community—the undergraduate medical student. My son is now in third year medicine preparing for his Seconds, and as I survey his class work I must say I am grateful that I graduated in 1924 and have for 27 years been able (I hope) to do some useful work in the sphere of general practice. I glance at a book *Statistical Calculation for Beginners*. The preface is good, "No assumption of mathematical ability on the part of the reader is made." I open it at random (p. 56):

The correlation between X and Y with the influence of Z removed is then given by the formula

$$r_{xy.z} = \frac{r_{xy} - r_{xz} \cdot r_{yz}}{\sqrt{1-r^2_{xz}}\ \sqrt{1-r^2_{yz}}}$$

and so on, and these are very simple hieroglyphics indeed compared to what follows. I refrain from further examples, as no typist in Britain could cope with them.

Now, Sir, what earthly good is this going to be when you are confronted with an antepartum haemorrhage in a kitchen bed or a cardiac collapse at a political meeting? It is pathetic to see good lads anxious to get on with their regional anatomy and with the fundamentals of physiology having to waste their time and mental energy on this.

Let postgraduates who are either so eccentric or so enthusiastic about statistics as to love this kind of thing drink their fill of it. I am quite sure that 90% of us who suffer the burden and heat of the day at our appointed tasks are simply allergic to it—and I hope we manage to do our work honestly and well in spite of our shortcomings.

I sometimes wonder if men like Lister, Macewen, and Rutherford Morison would have made the grade if this had been in their curriculum. Thank heaven it was not.

I hope someone who can speak on a higher level than I can will take this matter up, and, to extend the quotation of Mr. W. Grant Waugh, "save the sanity of the medical student, physician, or surgeon who does not understand 'these damned dots.'"—I am, etc.,

Glasgow. ANDREW S. BARR.

Counterblast

SIR,—Mr. W. Grant Waugh's remarks (November 3, p. 1088) require comment. There is, indeed, some truth in his censures. The doctor who turns to science is in a difficult position. His training in many ways is far from scientific, for the clinical and scientific approach to a problem are very different. The scientific method is careful, cautious in its exploration of new territories; it demands complete evidence for even the smallest advance. Yet the clinician, in the very nature of things, must reach conclusions and make decisions of the highest importance on the flimsiest of evidence. Moreover, the successful implementation of those decisions is influenced in large degree by his personality.

The things of which Mr. Waugh complains are, in fact, not the fault of the scientific method, but the inevitable effects of clinical training. How often have we seen the cerebral exaltation which results from years of god-like existence in the clouds of consultant practice, the man with a professed contempt for all who are more ignorant than he—which, as he is almost certainly surrounded by an impenetrable shell of self-importance, probably includes most of his fellow-beings. As for the "humanistic" (the word is Mr. Waugh's) values, their absence results far more from that same self-importance than from any scientific or "pseudo-scientific" attitude. It is true that science can be made into a peg on which to hang inhumanity, but inhumanity is not a result of science, and a lack of understanding of patients as individuals was just as apparent 20 years ago as to-day.

Medical practice cannot be fully scientific. A good clinician must be something of a gambler. Yet if medicine is to progress it should apply the results of scientific investigation. The arts of medicine have been tried and have given of their best. The real hope for advance lies in the laboratory rather than at the bedside. Yet the task of the medical research worker is hard. With the clinical half of his brain he must be ready to make his conclusions on minimal evidence and act decisively; with the other half he must be cautious in his approach to evidence, weigh his facts carefully, and be prepared to creep rather than run. He should remember that a medical qualification is not in itself an adequate apprenticeship to the scientific method. He should freely seek advice from whatever source is most appropriate, and his publications should be clear and free from false pretensions.

With all this in mind the present standard of medical publications is surprisingly high. The best hope for further improvement is to be found, not in the elimination of dots and dashes or the condemnation of statistics, but in the application of even more rigorous scientific standards, in ruthless self-criticism, and ruthless honesty on the part of those who publish research findings.—I am, etc.,

Bristol. JOHN GRAYSON.

What Happens in Pre-eclampsia

SIR,—Drs. B. E. Miles and H. E. de Wardener have joined issue (October 20, p. 976) on three points in my letter of September 29 (p. 797).

In dealing with my statement that plasma pentose possibly reflected a degree of glomerular ischaemia they draw attention to the fact that the transient hypertension and fall in glomerular filtration rate during infusion of adenylic acid are followed by a reverse change in the post-infusion phase. Bing *et al.*[1] give figures to show that in the case of muscle adenylic acid infusions this substance almost disappears from the blood stream within two minutes of stopping the infusion. The post-infusion phase is therefore synonymous with a circulation devoid of adenylic acid, and it is obviously irrelevant to our discussion, wherein we are considering its continuing presence indicated by the increased plasma pentose levels. The authors of the article state that "as long as the blood pressure remains above 70 mm. Hg (in their animals) reduced filtration can probably be attributed in part to some degree of afferent arteriolar constriction," and it was this factor in the experiment that I invoked as possibly reflecting a degree of glomerular ischaemia. The context of my letter amply indicates that the shut-down is considered due to a nervous reflex essentially, with adenylic acid possibly contributing to its maintenance.

The "Oxford shunt" includes in its mechanism three factors: first a gradual constriction of the renal artery; next, closure of the cortical glomeruli, layer by layer, from surface to medulla, which increases the obstruction to the intra-renal blood flow, eventually reaching a threshold in pressure sufficient to exceed the critical opening pressure of the vessels of the juxta-medullary nephrons, and in so doing providing an alternative and expansive bed for the blood stream therein. At this stage the rate of blood flow through the organ may even be enhanced, and it is this state of the renal circulation which I believe is to be found in cases of pre-eclamptic toxaemia. Eventually increasing spasm of the renal artery counters this effect on the flow. The *p*-amino-hippuric (P.A.H.) clearances, when based on an assumed complete extraction, indicate the plasma supply to tubules, whereas the same clearance when corrected by the observed extraction figures indicates the blood flow through the organ. The difference in value can provide a measure of the circulation in renal tissue which is non-nephronic—and could estimate the degree of shunt.

In confirmation of this concept I would cite Black and Saunders,[2] who state that "appropriate (sciatic) stimulation in some animals leads to profound alterations (reduction) in P.A.H. and inulin clearances . . . moreover, in similar circumstances the extraction of P.A.H. . . . is impaired even when the *renal-vein blood flow is in the normal range*"; also Moyer *et al.*,[3] who present a table in which it is shown that the renal blood flow is definitely increased in dogs when sciatic stimulation is first commenced. Later stages of their experiment (after two hours) are dealing with a very late stage of the shunt, when it is not surprising that there is considerable curtailment of the renal blood flow. The experiments of Insull *et al.*[3] were performed on considerably shocked animals, anaesthetized, with excised gastro-intestinal tracts, with abdominal aorta and inferior vena cava ligated above their bifurcations, with cannulated carotid arteries, and in whom the majority of the kidneys examined did not show diversion of the blood stream. They cannot possibly provide control figures under these circumstances for comparison, nor can they be germane to our inquiry of the blood flow during the "shunt."

Finally, contrary to Drs. Miles and de Wardener's statement, there is much evidence to indicate that there is a reduction of blood flow in the cortical tubular tissue in pre-eclamptic toxaemia. In normal pregnancy Welsh *et al.*[4] give a figure of 631 ml. "diodrast" clearance and 970 ml. uncorrected renal blood flow; whereas in toxaemia Chesley *et al.*[5] indicate that the diodrast clearance is 554 ml. Corcoran and Page[6] for three groups find the uncorrected blood flow 688 ml., 853 ml., and [989 ml.]. Dill *et al.*[7] give

[680 ml.] as diodrast clearance and 905 ml. for uncorrected renal blood flow, and Kenney *et al.*[8] a mean renal plasma flow of 420 ml.

In all the figures quoted—except for the two bracketed—my contention that a cortical ischaemia of varying extent exists in pre-eclamptic toxaemia is borne out, and the speculations provided in my letter may well therefore be considered against this extended background, especially as the marked accompanying reduction in the glomerular filtration rate together with these attendant circumstances defies an alternative haemodynamic interpretation.—I am, etc.,

London, W.1. J. SOPHIAN.

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Sulphamerazine Dangerous

SIR,—I am surprised that nobody has yet written a word in defence of that much-maligned drug sulphamerazine. I have used it almost exclusively since it became available, and have yet to experience any ill-effects whatsoever. It must, however, be administered in the correct dosage, and failure to do this probably accounts for most of the trouble experienced. Dr. W. Brand (October 13, p. 913) administered 0.5 g. every six hours to a child of 5, whereas the manufacturers' suggested dosage is 0.5 g. every 12 hours. I consider sulphamerazine the ideal sulphonamide for use in general practice because it only has to be administered every 12 hours to children in order to maintain a satisfactory blood level; sulphonamides which have to be administered every four or six hours necessitate the giving of a dose in the middle of the night. I often found that this night dose was "forgotten" by a harassed and over-tired mother.—I am, etc.,

Malvern. A. L. BROWN.

SIR,—May we endorse Dr. E. C. Atkinson's warning (September 15, p. 674) of the danger to the kidney from sulphamerazine? With the approach of winter it seems important that both the risks of the drug and the value of a simple measure for the relief of anuria caused by it should be generally recognized. In the past twelve months we have seen six children with anuria or oliguria due to sulphamerazine, apart from cases of haematuria alone. The cases were:

1.—Age 4½ years. Five days before admission to hospital he developed tonsillitis and was given "cremomerazine" 2 dr. (7 ml.) followed by 1 dr. (3.5 ml.) six-hourly. Haematuria developed after 24 hours and he was admitted with 48 hours' anuria and passed no urine for a further four days. This child was very ill, with blood urea of 327 mg. %, and seemed likely to die.

2.—Age 4. This child had been feverish for a week and was given a single dose of three dessertspoonfuls of cremomerazine. The next day he developed haematuria and was admitted to hospital. On the fourth and fifth days his urinary output was reduced to 6½ and 7 fluid ozs. (200 ml.). Spontaneous diuresis followed.

3.—Age 3 years 7 months. One week before admission to hospital this child became feverish and was given a course of cremomerazine (dosage not recorded). He was admitted with three days' anuria and was at first treated with a restricted fluid intake and a glucose-arachis-oil mixture. On the third day cystoscopy was performed; both ureteric orifices were found to be oedematous and it was impossible to catheterize the ureters. Diuresis began within three hours of cystoscopy and he made a rapid recovery.

4.—Age 3. Four days before admission he was given cremomerazine 1 dr. eight-hourly for three days for measles. He was admitted with 18 hours' anuria. Diuresis began within eight hours of a bladder wash-out and he made a rapid recovery.

5.—Age 3 years 5 months. Six days before admission he was given sulphamerazine 1 tablet (0.5 g.) thrice daily for three days (10 tablets in all) for measles. He was admitted with 36 hours' anuria. Again diuresis began within eight hours of a bladder wash-out and he made a rapid recovery.

6.—Age 8. Five days before admission he developed a sore throat and was given sulphamerazine 1.5 g. followed by 2 dr. (7 ml.) cremomerazine twice daily. He was admitted with 24 hours' haematuria. Bladder wash-out was performed on admission, but anuria developed. At cystoscopy 24 hours later the right ureteric orifice was normal: the left was red and oedematous, and resistance was felt on passage of a catheter up the left ureter. The pelvis of the left kidney contained a considerable quantity of urine. Diuresis began within eight hours of cystoscopy and he made a rapid recovery.

There was no doubt from the course and the urinary findings of these cases that they were indeed instances of sulphonamide anuria and not of acute nephritis with suppression of urine. During this period we have met no comparable renal complications from any sulphonamide other than sulphamerazine. It should be noted that the dose which may cause anuria does not need to be excessive. The palatability of cremomerazine, however, the small volume of suspension in which the dose is contained, and the notorious variability in the capacity of teaspoons may result in the prescribed dose being exceeded. The difficulty of getting sick children to drink and their tendency to vomit, particularly when they have sore throats, also mean that the urinary output may be inadequate.

The findings at cystoscopy in Cases 3 and 6 support the belief that this type of anuria is due to blockage of the lower ureters by crystalline deposits and provide a rationale for the first line of treatment—namely, washing out the bladder through a rubber catheter. Joekes has declared that urinary flow in sulphonamide anuria can often be quickly restored by lavage of the bladder, and this simple procedure has seemed to us to be of great value.—We are, etc.,

S. A. MORTON.
London, E.2. R. H. DOBBS.

SIR,—In the course of correspondence on this subject Dr. W. Brand (October 13, p. 913) asks, "How dangerous is sulphamerazine to children and what is the incidence of complications? Should it be used in domiciliary practice?"

I should like to add to my original letter on this subject information which has recently come to hand from a well-known firm of manufacturing chemists. The Medical Information Division of this firm informs me that they have received reports of a considerable number of cases of sulphamerazine crystalluria which have not appeared in the medical press, and their collection includes fatalities arising from this cause. The dangers and necessary precautions to be taken when using sulphamerazine are clearly set out in the booklet issued by the firm in question.

There are, in fact, three pages devoted to poisoning arising from the administration of sulphamerazine. Picked out in bold type is the statement that "the most important precaution to take in the administration of sulphamerazine is the maintenance of a high fluid intake. The fluid intake should not be less than five pints in 24 hours in an average sized adult, with a urinary output which does not fall appreciably below half this amount. If there is excessive fluid loss from diaphoresis, vomiting or diarrhoea, the fluid intake must be correspondingly increased." Of course, the booklet stresses the fact that the dosage for children and adults is much smaller than with the other sulphonamides. Thus, for a child of between 3 and 10 years of age, it is recommended to give 1.5 g. initially followed by 1.0 g. every 12 hours.

From this information and from the correspondence which has appeared in the *Journal* on this subject I think one can be left in no doubt that the administration of sulphamerazine to a child in its home is fraught with danger. That the danger lies partially in careless over-dosage and/or insufficient fluid administration must be freely admitted. But these are factors which arise from the usual human element, and in my opinion it is because of them that sulphamerazine is so dangerous in the home. I think one must feel very concerned to read that several fatalities have occurred from the use of sulphamerazine and that they have not been reported in the medical press. This alone should cause any intending prescriber to consider whether there is not an equally good substitute in the sulphonamide field when he intends to prescribe sulphamerazine for a child.—I am, etc.,

Sheffield. E. C. ATKINSON.

Deafness from Dihydrostreptomycin

SIR,—I should like to support Dr. R. W. Biagi's plea (September 15, p. 651) to return to the use of streptomycin instead of the dihydro- compound, as the latter appears to be more likely to cause deafness. Within the past few weeks I have seen four cases of severe deafness following prolonged therapy with dihydrostreptomycin. They affected three out of four children under treatment for tuberculous meningitis and miliary tuberculosis. The fourth case was an adult suffering from renal tuberculosis. All these cases showed marked nerve deafness. and the last case was totally deaf in one ear. Response to heat stimulation was also markedly diminished or absent in all these cases, but none of them remembered having noticed vertigo, and there was no spontaneous nystagmus present. Although the vestibular part of the inner ear was affected as well as the cochlear, the warning signal of giddiness, noticed often during the use of streptomycin, was absent. The number of cases I have seen is insufficient for statistical evaluation, but they leave little doubt that dihydrostreptomycin is toxic to the auditory apparatus.—I am, etc.,

Rugby. P. E. ROLAND.

SIR,—So far as the incidence of deafness is concerned, the results obtained in the treatment of tuberculous meningitis with dihydrostreptomycin in Sheriff Hill Hospital, Gateshead, are in line with the experiences of Dr. R. W. Biagi (September 15, p. 651) and subsequent contributors to the *Journal*.

Since the autumn of 1948, treatment of miliary tuberculosis in 32 patients with the new antibiotics has been completed. In 30 of these meningitis was present. At first, streptomycin was used systemically and intrathecally, but at the end of 1949 a satisfactory trial of dihydrostreptomycin in two patients suffering from a relapse led to its adoption for routine use. Two patients suffered from miliary tuberculosis of the lungs only, and in them the drugs were used systemically.

The patients fall into three small groups. The first nine patients, including one with miliary disease of the lung, were all treated with streptomycin alone, and there were two survivors, both without sequelae. A second group of five patients has had successive or mixed courses of streptomycin and dihydrostreptomycin. Four have survived, but two of these are deaf and one has vestibular damage. In the last group of 18 patients, including one with miliary tuberculosis of the lungs only, treatment was entirely with dihydrostreptomycin and there have been 11 survivors, eight showing some impairment of hearing.

In this hospital, lengthy courses of streptomycin and of dihydrostreptomycin have been given systemically to the two patients with miliary disease of the lungs and to a number of other cases of pulmonary and bone and joint tuberculosis, but no toxic sequelae have been noted. Damage to the auditory nerve has been limited to patients who had been given dihydrostreptomycin intrathecally, and has been most severe in young children. In adults and adolescents treated by dihydrostreptomycin intrathecally, deafness was heralded by a buzzing tinnitus and has not been absolute. In children the onset of deafness tended to be sudden, and recently was first noticed in a 2-year-old child three months after the conclusion of intrathecal treatment with dihydrostreptomycin in moderate dosage.

Although we feel that these lives have been saved at the expense of hearing, we have now reverted to streptomycin in the intrathecal therapy of tuberculous meningitis.—I am, etc.,

Gateshead. JAMES GRANT.

Septic Thrombophlebitis of the Cavernous Sinus

SIR,—Septic thrombophlebitis of the cavernous sinus is no longer almost always fatal, but those who recover may be imbecile. Discussion with colleagues overseas confirms this experience. To rely wholly upon antibiotics is unwise. The septic thrombus should be evacuated by methods described elsewhere (Lodge, W. O., *Boll. Mal. Orecch.*, 1951, 69, 199) as soon as the diagnosis is established.—I am, etc.,

Halifax. WILLIAM O. LODGE.

Abacterial Cystitis

SIR,—This latest article on abacterial urinary tract inflammation by Drs. J. W. Czekalowski and G. O. Horne (October 13, p. 879) prompts me to record a personal experience.

I suffered from chronic urinary infection (*Bact. coli*) in childhood, and a static hydronephrotic condition remained, although the urine had been rendered sterile with mandelic acid. This symptomless state of affairs persisted for many years, routine laboratory examinations of the urine revealing no abnormalities. However, some four years ago symptoms of cystitis suddenly recurred, together with the passage of large amounts of phosphates in a strongly alkaline urine. No organisms or pus could be detected in the urine, and treatment with sulphonamides was of no avail. All attempts to acidify the urine were also unavailing, and the symptoms waxed and waned until the beginning of this year. It was noticed that the condition seemed worse in the summer, and when residing in an area where the water was very hard. All the usual treatments for phosphaturia were tried, without success. At times the local pain due to passage of large deposits of phosphate crystals was so severe as to necessitate analgesic drugs. Frequent laboratory urinary examinations during this period failed to reveal any abnormality except deposits of triple phosphate crystals.

Having never suffered from whooping-cough in childhood, it was not surprising that I contracted the disease during the heavy epidemic last winter. Diagnosis was delayed, however, for some four weeks owing to the minimal symptoms. Chloramphenicol, 0.75 g. thrice daily, was then taken for eight days, with no effect on the whooping-cough. However, the symptoms of phosphaturia disappeared after two days' treatment, and the urine became acid for the first time in four years. This unexpected result has continued to the present time, with no relapse to the former condition, although no further chloramphenicol has been taken.

It can only be concluded that what had been regarded as a biochemical abnormality was in fact an abacterial infection. I can think of no other explanation of the dramatic cure with chloramphenicol.—I am, etc.,

Twickenham. DAVID WHEATLEY.

Chronic Ill-health in Childhood

SIR,—The school medical officer is among the many who will have read with interest and profit Dr. J. J. Kempton's article (October 13, p. 903), in which, however, he made no reference to vaccine therapy. Well aware that in mentioning this I may deserve a well-merited rebuke, I hasten to acknowledge fully the risks of merely aggravating the child's condition by the unwise and untimely use of vaccine.

I have, however, seen among children suffering from chronic bronchitis dramatic and lasting improvement following injections with polyvalent anticatarrh vaccine. I have no worth-while figures, and would be among the first to criticize attempts to generalize from isolated instances. Perhaps the cases I have seen would have improved without vaccine. Possibly the preliminary trials with small fractions of the normal dose, in order to determine the danger or otherwise of aggravating the case, is a procedure which a busy practitioner would not contemplate. For psychological reasons alone it is desirable that the number and variety of injections administered to children shall be kept to the lowest possible. No doubt other good reasons could be mustered against the use of vaccines in bronchitis.

In spite of all this, however, there remains the feeling that vaccines should not be dismissed as having no place at all in the treatment of the chronic bronchitic, unless of course statistics can be marshalled to discredit the procedure. For one thing, whereas Dr. Kempton has placed general treatment on a foundation of rest, nasal treatment, and exercise, it will be recognized that in all too many cases it is not possible to ensure the necessary regularity in the regime or the strict adherence to its detail. The family doctor and the school medical officer may thus be obliged to continue their search for alternatives.

It would be interesting to know what organisms are the worst offenders, and to what extent they sensitize the patient against efforts to build up an artificial immunity. The school doctor is interested in the matter for a further reason. Education authorities are alive to the need for the fullest attendance in school. When may the chronic bronchitic return to

school without the risk of being a focus of infection to other children? It is with the preventive aspects in mind that the school medical officer would probably note with particular interest any advances in vaccine therapy which the physician is able to report.—I am, etc.,

Edinburgh. S. M. MUSGRAVE.

External Cephalic Version

SIR,—I believe that external version under anaesthesia is seldom indicated, and I suggest to Dr. Derek Freeth and Mr. J. S. MacVine (October 13, p. 881) that in the majority of cases in which the breech can safely be turned under anaesthesia it can also be turned without it if care is taken to ensure that the patient is relaxed and mentally at ease before the operation is undertaken.

If version without anaesthesia is unsuccessful, and no doubt exists that the pelvis is adequate in size, elective breech delivery should be planned, preceded by induction of labour at between 38 weeks and term. If this is done and the actual delivery is conducted by an obstetric team of adequate competence, this being important whether the patient is primigravid or multiparous, it should not be found that the corrected foetal mortality is higher than 1–2%. This figure compares not unfavourably with the foetal mortality due to version of 1.4%. It is interesting that this figure is not higher in view of the fact that Messrs. Freeth and MacVine apparently regard vaginal bleeding during the operation of version (which can only be due to some degree of placental separation) with comparative equanimity.

If the better results which can be obtained by carefully planned breech delivery are admitted, why subject the mother to the additional discomfort and slight risk of general anaesthesia ?—I am, etc.,

Glasgow, S.W.1. JAMES MAIR.

Coma Due to Acidosis

SIR,—Dr. R. M. J. Harper (October 13, p. 909) wanted to know of any other cases of acute ketosis uncomplicated by diabetes producing coma.

I have seen at least three such cases of healthy children aged 3 to 8 years who had to be admitted to hospital or nursing-homes in coma. All these children had the same type of history, vomiting continuously for 20–30 hours, first food, later bile-stained mucus; increasing restlessness, nausea and headache; followed by drowsiness, then coma. In all cases the children were dehydrated, smelt strongly of acetone, urine full of acetone, blood sugar normal; two cases had severe hyperpnoea.

With the usual treatment, stomach wash-out with bicarbonate solution, intravenous glucose and Ringer's solution, the children improved steadily and were soon able to sip drinks of glucose and bicarbonate by mouth and later suck glucose sweets. Within a few days they were eating a high carbohydrate and low fat diet. All made an uncomplicated and complete recovery.

I have seen numerous other children who had not got to the stage of coma but had been vomiting 12–24 hours; who were restless, irritable, complaining of nausea and headache. These early cases usually responded to treatment with sips of glucose and bicarbonate, also sodium citrate every four hours. A few needed stomach wash-out, but none needed intravenous therapy. Most of these cases had histories of recurrent attacks of acidosis.—I am, etc.,

Torquay. MADELEINE R. EPSTEIN.

College of General Practice

SIR,—The history of the Society of Apothecaries is the history of the rise of general practice in this country; and the Court of Assistants are following with sympathetic interest the correspondence now appearing in your *Journal*. As has been pointed out in the *Lancet*, the Society was largely concerned in the discussions which took place in 1847–9, and still maintains an active interest in general practice, the L.M.S.S.A. being broadly designed to meet the requirements in this field.

The Court are fully alive to the importance of establishing a College of General Practice, and—although I cannot at this juncture say to what extent the Society, if called upon to do so, would be able to sponsor so far-reaching a scheme—I can say that they would be willing to help; which, under the terms of their ancient Charter and with their long experience as an examining body, they are well qualified to do.

The correspondence shows that there is difference of opinion about what should qualify for Membership of the College—but I should like to state that, if it were founded under the aegis of this Society, it would not be necessary for Members to take up the Livery, as was suggested by Dr. Harold Leeson. The proposals do not appear to impinge upon the functions of the Royal Colleges—and it would seem fitting that the historic home in which General Practice was given birth and nurtured should become the headquarters of its College.—I am, etc.,

Worshipful Society of Apothecaries of London. G. ROCHE LYNCH, Master.

SIR,—Drs. F. M. Rose and J. H. Hunt (October 13, p. 908) have placed general practitioners in their debt by initiating correspondence in the *British Medical Journal* and *Lancet* on this subject. Dr. A. Talbot Rogers makes a good point (*Lancet*, October 20, p. 736) when he suggests that it should be a College of General Practitioners and not of General Practice. This would conform to the precedent set by the three Royal Colleges.

The original Fellows of the College of General Practitioners would have to be self-appointed; that is unavoidable. Fellowship should be restricted at first to senior G.P.s of a certain number of years' standing and of good academic qualifications. I should like to see the founder Fellows of the College supported in their application for admission by, say, 10 proposers and seconders, of which one should be an F.R.C.P., another an F.R.C.S., and a third an F.R.C.O.G., and he should be supported by at least three fellow practitioners of his area of practice. This would have to be liberally interpreted.

Once the College is established, admission should be by membership, followed later by fellowship. How are the members to come in? Will they have to pass an examination, or be invited to become members? Regulations for admission should be such that the conferring of membership or fellowship would be recognized by the general public as a mark of professional distinction. Dr. L. N. Jackson (*Lancet*, October 20, p. 736) makes a very sensible contribution in this respect.

I do not know how far matters have progressed as regards founding the College. I presume that the founding committee will have the assistance of the three older Colleges to help drafting regulations and by-laws. The R.C.O.G., as the newest College, could probably offer some valuable suggestions about the procedure of founding. The G.M.C. would also have to be represented on the founding committee.

I feel strongly that medical students are not given a correct approach to general practice. When I was at hospital 30 years ago I formed the opinion that G.P.s were despised by the majority of the teaching staff and, therefore, by the students. There should be a Chair of General Practice at all universities and readerships in all hospitals. Medical students should, whether they like it or not, have to attend the practice of a G.P. for a week or a fortnight so as to sweep away the cobwebs of prejudice. It should be the duty of all members and Fellows to take a certain number of students per year for this introduction to the art (for art it certainly is).

The postgraduate education of G.P.s should be in the charge of the College, aided, of course, but not supplanted by the other older Colleges. Quite frankly, the older Colleges are abysmally ignorant of what general practice is like and what it needs.—I am, etc.,

London, E.17. ST. GEORGE B. DELISLE GRAY.

SIR,—Drs. F. M. Rose and J. H. Hunt in their letter (October 13, p. 908), and individual memoranda of evidence to the General Practice Review Committee (*Supplement*, October 27, p. 173) have made out an unanswerable case for a College of General Practice. The only possible arguments against such an institution are the difficulties in the way of establishing a foundation. Everything that is worth while is worth the struggle and hard work necessary for its attainment. It is up to the general practitioners themselves to start work at once to achieve a College through which they can authoritatively express their views and by which they may be guided on the performance of their work. The need for a body which takes its place in equality with the other great colleges of the profession is self-evident.

Many of us are getting rather tired of the frequent attempts to denigrate us in the eyes of our colleagues and the public. Why should we cry ourselves down? Surely we all realize that the standard of practice to-day is considerably higher than it was 20 years ago. It is only the standard of the last three years which has not improved. Under pressure of increased work and smaller remuneration we have found it harder to maintain that level of excellence to which we are accustomed. The volume of support for the proposal of Drs. Rose and Hunt is an indication of the desire to maintain practice at a high level of efficiency.

One way in which the proposed college could be of help to general practice and to medicine as a whole has not been mentioned. Throughout the country there is a mass of clinical matter as yet unstudied which can only be studied by the general practitioner. A College of General Practitioners could and should encourage and foster research in general practice. Should there not be fellowships in research for general practitioners? Could not research assistants be offered to practitioners desirous of embarking on special lines of study? Surely in such a way the College could make their real contribution to the knowledge of many diseases and syndromes at present little understood. The contribution which could be made is well emphasized by the letters from the chairman and secretary of the Glamorgan Local Medical Committee and from Drs. J. C. R. Morgan, E. G. Jones, and D. R. Morgan (October 27, p. 1029). These general practitioners were the observers of an outbreak of tuberculosis which might but for their swift action have been disastrous.

It may be argued that general practitioners have little interest or time for research and that they have not the necessary training. The suggestions I have made would go a long way towards providing the time. From personal knowledge I know that many practitioners would welcome the opportunity of taking part in schemes of research. The average practitioner lives in professional isolation and does not have the opportunity of developing his talents in this direction. When it comes to discussing his clinical material he is a shy bird and rather apt to underestimate his own ability. The membership or fellowship of a College of General Practice would indeed give him that self-assurance which he so often lacks.—I am, etc.,

Dartmouth. R. M. S. MCCONAGHEY.

SIR,—During the war I discussed the need for providing a higher qualification for general practitioners with a few of my friends, including Sir Allen Daley. My own idea was that there should be an examination of a special character which could only be taken at least five years after the candidate had entered general practice. There were two alternatives which were considered. The first was that a degree of M.D. might be granted by the University of Reading, which has no medical faculty, but inquiries in this direction proved fruitless. As an alternative it was considered practicable that an Institute of Medical Practitioners be established by incorporation, in the same way as the Royal College of Obstetricians and Gynaecologists and the Faculty of Radiologists, although the former subsequently obtained a Royal Charter.

I recollect with some amusement that I sent my old friend Dr. Gordon Ward, of Sevenoaks, model examination papers which I considered suitable, including tricky problems associated with social medicine. Unfortunately it was not considered that the time was opportune for such a project to be developed, and I am delighted to read in the columns of the *British Medical Journal* that the whole question is now again being considered. I still prefer the title which I suggested to the one appearing in your columns.—I am, etc.,

London, S.E.9. CHARLES BROOK.

SIR,—We have had a most encouraging response to our letter of October 13, and many helpful suggestions have been made about the proposed foundation of a College of General Practice. During the next few months it is possible that this subject will be discussed at meetings of general practitioners throughout the country. Once again may we use the hospitality of your columns to ask the secretaries of such meetings to send us detailed reports of what is said?—We are, etc.,

99, Fylde Road, Preston, Lancs. F. M. ROSE.
54, Sloane Street, London, S.W.1. J. H. HUNT.

Chronic Otorrhoea and Chloramphenicol

SIR,—I read with interest the report of Mr. Roland S. Lewis and Dr. J. D. Gray on the treatment of chronic otorrhoea with chloramphenicol (October 20, p. 939).

Present methods of conservative treatment for chronic suppurative otitis media are legion, many are unscientific, many are worse than useless, and their employment suggests ignorance of the underlying pathology of this common condition. The important paper to which I refer demonstrates a logical method of treatment based on knowledge of the flora almost invariably found. I make no comment on the first group of cases dealt with, but I can endorse the remarks relating to the efficacy of chloramphenicol treatment in operation cavities resulting from fenestrations and radical and epitympanic mastoidectomies. Many of these cases have been treated with prolonged courses of systemic penicillin, and the organisms most frequently found are coliforms, *Proteus vulgaris*, and *Ps. pyocyanea*.

For a period of about six months only I have been using chloramphenicol in these cavities, but the results in this short time have been most gratifying. The method employed has been the meticulous mopping of the cavity followed by cauterization of granulations with trichloracetic acid. Chloramphenicol powder is then insufflated until the walls of the cavity are coated with a fine "frost." This treatment is carried out by the otologist two or three times weekly, most of the cavities dealt with being dry within two weeks from the commencement of treatment.

Chloramphenicol for the chronic ear should prove to be a strong nail in the deserving coffin of "penicillin ear-drops" and other illogical forms of treatment.—I am, etc.,

London, W.1. E. H. MILES FOXEN.

Treatment of Plantar Warts

SIR,—The mention of warts, and then allergy, in two consecutive letters in your issue of August 18 (p. 419) prompts me to send in a report of two interesting cases seen lately. The first was a small boy, from a known allergic family, with radiating lines of warts round his mouth and many more on his hands. Seeing the warts like this, and knowing his family history, I put him on to "anthisan" tablets, two a day, and all his warts disappeared in a week—hard and solid though they had seemed. This child came from a red-headed family which also includes two asthmatics and a hay-fever case.

A week or two later a frail, pale, red-haired ex-sailor came in with many hard warts over his hands which he had had for as long as six years. I put him on to the same dose of the antihistamines—going on his appearance alone—and all his warts were gone in a fortnight.—I am, etc.,

St. Neots, Hunts. C. F. PATTERSON.

Calcium Pantothenate and Burns

SIR,—In view of the interesting correspondence precipitated in the columns of your *Journal* by the report of Dr. A. E. Milne *et al.* (July 14, p. 117) on the use of antihistamines in the treatment of burns, including that of Dr. S. B. Stoker on local heparin therapy in neutralizing the toxic products of burns (August 11, p. 360), we would like to add our experimental findings on another substance which in this case we found effective in significantly reducing mortality due to burns. Calcium pantothenate, when dissolved in physiological saline and administered intraperitoneally in doses of 100 mg./kg. body weight before a lethal burn obtained by immersing 90% of the body surface of rats in water at 70° C. for 15 seconds, increases the survival rate in rats as compared to controls receiving an equal volume of physiological saline solution. Statistical treatment of the number of animals surviving at 12, 24, 48, and 72 hours after the standardized burn indicated that at the 1% probability level calcium pantothenate/saline solution had a significantly greater protective action than saline alone. With equivalent doses of methionine dissolved in saline and given 1½ hours before the burn, the effect was the same as with saline alone, although Hazan and Treadwell, using the technique we adopted, reported a significant effect at higher doses of methionine (*Proc. Soc. exp. Biol. N.Y.*, 1948, **68**, 684).

The mechanism of action has not as yet been determined, nor is it known whether the effect is specific for this vitamin. It may be that in the extensive metabolic changes of burn shock the coenzyme A concentration of certain tissues becomes critical, thus increasing the requirement of pantothenic acid for binding into the cofactor. It would be of some interest to study clinically the effect of this substance in burn therapy.—We are, etc.,

L. P. MUNAN.
A. EINHEBER.
George Washington University, Washington, D.C.

POINTS FROM LETTERS

Treatment of Migraine

Dr. N. N. IOVETZ-TERESHCHENKO (Georgetown, British Guiana) writes: With reference to your annotation on the treatment of migraine (September 1, p. 538) and the letters from Dr. H. C. Stewart and Dr. H. S. C. Wight (September 15, p. 673) it is rather surprising that no mention is made of the fact that ergotamine tartrate is more efficient when allowed to dissolve under the tongue than when swallowed, and that an injection of atropine prevents the nausea which sometimes occurs with light dosage or in sensitive persons.

Cigarette Smoking and the Hands

Dr. J. G. BENNETT (Woodley, Cheshire) writes: The article by Dr. J. T. Shepherd (October 27, p. 1007) which stresses the connexion between dead hands and tobacco addiction bears on my own case. I am 63 years old, and I have smoked on an average between 20 and 30 cigarettes daily since the age of 18. Up to the approximate age of 60 I felt few ill effects, but for the last three years I have suffered increasingly from numbness and tingling of the fingers on rising, which gradually got so bad that I was unable to fasten my collar without pain. . . . With great fortitude I stopped smoking for a whole month. At the end of a fortnight the dead hands were normal, I had no morning cough or sputum, and I rested like a baby. I then began to smoke again, 10 to 12 cigarettes daily. As a result the same syndrome, in modified form, is creeping on me again.

A Plain Word

Dr. I. GEIKIE-COBB (London, N.W.1) writes: In commenting on my criticism of your use of the word "anatomized" you say that it is no new invention. I did not maintain that it was. I am well aware that it is not: indeed, it is to be found in the *O.E.D.* as a "v.t. & i." I said, and with respect I repeat, that it is an ugly word and no writer with an ear for language should use it.

Correction

Through an error by the printer the word "anatomized" was unfortunately substituted for "atomized" in the final printing of the letter "Primary Atypical Pneumonia" from Professor C. H. Stuart-Harris last week (November 10, p. 1152, last line but one of para. 1).

Obituary

Dr. EDWARD SIDDALL JACKSON, of Carnforth, Lancs, died suddenly on September 13. His death brought to an end over 100 years of medical practice in the same town by his father, grandfather, and great-grandfather. The younger son of the late Dr. E. S. Jackson, he was born in 1892, and educated at George Watson's College and Edinburgh University, at which he graduated M.B., Ch.B. in 1921. His medical studies were interrupted by service with the R.F.A. from 1914 to 1918. He then joined his father in practice, and remained in Carnforth until his death. He was essentially a family doctor. Having been born and brought up among his patients, he knew them, their parents, and their grandparents, and, later, their children and grandchildren. It was natural that he was esteemed as a friend as well as a doctor, and his cheerful disposition, kindly nature, and depth of sympathy endeared him to all who knew him. His busy practice left little time for relaxation, but he nevertheless contrived to play cricket and rugby football in his younger days, and in later life to acquire a wide and intimate knowledge of trees and wild birds. On many occasions he has taken me by country lanes to point out an unusual tree or the haunt of a rare bird. To accompany him on a country visit was an education and a delight. His elder son was killed in 1945 at Luzon in the Philippines while serving with the American Army. Dr. Jackson is survived by his wife and younger son, to whom the deepest sympathy will be extended.—J. W.

Dr. HARRY PERCIVAL FOULERTON, medical superintendent of Broadmoor Asylum from 1926 to 1937, died in his sleep on October 15 in his 78th year. He returned to London that day after a three weeks' holiday, and seemed to be well. He received his medical education at St. George's Hospital, and took the Conjoint Diploma in 1897 and the D.P.H. (R.C.P.S.) in 1900. After holding appointments as casualty officer at St. George's Hospital and house-physician at the Royal United Hospital, Bath, he began a long and useful career in the Civil Service in 1900. He first served as a medical officer in Liverpool Prison and later at Holloway Prison until 1910. He was then appointed deputy medical superintendent at Broadmoor Criminal Lunatic Asylum. During the first world war he served as a captain in the R.A.M.C. with the late Sir John Baker, the medical superintendent, in charge of the insane German prisoners of war, who were detained in a special block of the institution. He became medical superintendent at Broadmoor in 1926 and retired in 1937. He then went to live at Yateley, in Hampshire, but during the last years of his life he lived in London. Foulerton made the care and treatment of the criminal lunatic his main life's work, and was peculiarly fitted for this difficult, exacting, and not infrequently dangerous task, meeting sudden emergencies with calm and unruffled precision. His prolonged experience made him a valuable colleague as one of the members appointed by the Home Secretary to hold a medical inquiry under Section 2 (4) of the Criminal Lunatics Act, 1884, and he approached the day-to-day problems with the reflection that many of his patients might never be fitted to return to life in the outer world. So far as possible, therefore, he endeavoured to fit each patient into the most appropriate and comfortable place in the institution which could be safely given him. Foulerton was well suited to country life and obtained much satisfaction in his appointment. He had two sons by his first wife. The sympathy of his former colleagues and contemporaries will go out to them and his second wife, the daughter of the late Major-General and the Hon. Mrs. Mitford, and her son.—W. N. E.

Dr. ALAN MCKINSTRY FLEMING died suddenly from a coronary thrombosis at his home in Nairobi, Kenya, on October 17, at the age of 56. He was educated at the University College School, London. Having enlisted in the

ranks in 1914, he served through the first world war, rising to the rank of captain in the Bedfordshire Regiment. He was wounded and won the *M.C.* After demobilization he entered the Middlesex Hospital, graduating M.B., B.S. in 1927 and carrying off several prizes, and held the posts of house-surgeon and house-physician. After a term of office as house-physician at the Brompton Hospital he joined the Colonial Medical Service in 1929 and was posted to the Mulago Hospital and Medical School, Kampala, Uganda, as lecturer in medicine. In 1933 he was invalided to England with pulmonary tuberculosis, but, recovering, held appointments at the Royal National Hospital for Diseases of the Chest, Ventnor, and at Ruthin Castle. In 1934 he married Miss Dorothy Coward, a former nursing sister of Mulago Hospital. He rejoined the Colonial Service in 1936 and organized tuberculosis work in Gibraltar until 1942, when he was transferred to Kenya. In 1945 he was flown to England because of ill-health, but he made a good recovery and was welcomed back to Kenya seven months later. In 1947 he was appointed senior medical officer in charge of the Medical Training School, Nairobi, and moved to the responsible post of senior medical officer, Nairobi, in 1949. His duties then included acting as medical superintendent of the fine large African hospital, which became the King George VI Hospital on February 16, 1951, when the new surgical wing was opened by Countess Mountbatten. Dr. Fleming's mature experience and sound knowledge of medicine admirably fitted him for this important post, in which he endeared himself to all his colleagues. An untiring worker for the B.M.A., Dr. Fleming was honorary secretary of the Uganda Branch in 1930, honorary secretary and president of the Gibraltar Branch from 1939 to 1942, and honorary secretary of the Kenya Branch from 1947 to 1949. Besides serving on the Cathedral Council in Nairobi, he was a valued member of the St. John Ambulance Brigade, a keen mason, and active in the British Legion. At the time of his death he was president of the Natural History Society of Kenya. At the funeral service, held in the cathedral, large numbers of all races gathered together to pay tribute to this man of sterling worth who, during his eventful life, had given such unstinted service. He is survived by his widow.—F. J. W.

Dr. FRANK SMALLPAGE HUNTER, who died in Bristol on October 25 at the age of 80, was born at Bacup, and studied medicine at Guy's Hospital and the Universities of Birmingham and Bristol. He qualified M.R.C.S., L.R.C.P. in 1925. He had already been associated with the medical publishing firm of John Wright and Sons, Ltd., and was later elected to the board of directors. He became supervisor of the medical books and journals published by the firm, and his services were very valuable not only to them but also to the authors whose books or papers were submitted for publication. He was an excellent proof reader, and gave a shrewd opinion on what was worth publishing and what was not. The *Medical Annual* for many years owed much to his suggestions and general supervision. Many readers of this and other of the firm's publications have been in his debt, probably without realizing it. He was of a quiet and retiring disposition, and an accomplished musician. He is survived by his wife, a son, and a daughter.

Dr. LEONARD BODLEY SCOTT, of the Indian Medical Service, and later medical officer of health of Blandford for many years, died at his home in Blandford, Dorset, on October 30 after a short illness. He was 74 years of age. The son of the late Dr. Thomas Bodley Scott, of Bournemouth, Leonard Bodley Scott won a scholarship to Christ's College, Cambridge, where he took first-class honours in the natural sciences tripos, and then, like other members of his family, he went on to St. Bartholomew's Hospital. After graduating M.B., B.Ch. in 1901 he entered the Indian Medical Service. He proceeded M.D. in 1905, and in the same year took the D.P.H. of the University of Oxford. During his service in India he was for a time on the North-west Frontier, and in 1919 his name was specially brought to the notice of the Government of India by the commander-in-chief for valuable services rendered during the first world war. In 1922 he retired from the I.M.S. with the rank of lieutenant-colonel and then settled in Blandford, where he remained in general practice till 1937. He was appointed medical officer of health of Blandford Borough and Rural District in 1922, a post which he held until the end of 1949. For many years also he was medical officer of the Wimborne and Cranborne Rural District, and for a short time during the second world war he acted as medical officer of health of Wimborne Urban District.

D. O. writes: Leonard Bodley Scott was a great "out-of-doors" man. At Cambridge he was awarded his half-blue for water polo. While at Blandford he did most of his visits in his extensive semi-rural district on his bicycle. He was greatly interested in rowing, and never missed Henley Regatta. His other hobbies were carpentry, at which he was an expert, and gardening. To all who knew him, both colleagues and patients alike, he was a very real friend and wise counsellor who will be sadly missed. We extend our deepest sympathy to his wife and three children.

Medico-Legal

RESTRICTIVE COVENANT UPHELD

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Under a partnership agreement dated February, 1945, Dr. Mark Bradford carried on the profession of general medical practitioner at Atherstone, Warwickshire, in partnership with Drs. I. E. Whitehill, A. D. Egan, and C. V. Spark. The agreement provided that any partner could retire on giving six months' notice in writing, that the continuing partners should have the option to buy his share, and that the retiring partner should not practise medicine within a radius of 10 miles of Atherstone Church for 21 years. In March, 1951, Dr. Bradford gave notice that he intended to retire, and that he intended thereafter to practise within the 10-mile radius, claiming that the restriction was void as being contrary to public policy. All four doctors were on the National Health Service lists of the Warwickshire and Leicestershire Executive Council.

Drs. Whitehill, Egan, and Spark exercised their option to buy Dr. Bradford's share, and brought an action in the Chancery Division of the High Court to restrain him from practising within the radius. The action was heard before Mr. Justice Danckwerts.[1] He decided that the 10-mile limit was necessary to protect the practice of the continuing partners, since a good number of the 13,000 patients on the partnership list lived between five and ten miles from Atherstone. Although the National Health Service Act, 1946, forbade the sale of practices, it did not prohibit restrictions of this kind being placed on retiring doctors. The restriction did not create a monopoly, and Section 1 of the National Health Service (Amendment) Act, 1949, had the effect of preserving covenants of this nature.

The restriction was therefore unaltered by the National Health Service Act and was not void as being contrary to public policy, and an injunction was granted against Dr. Bradford to enforce its terms.

[1] *The Times*, October 30.

Another step in the reorganization of nurse training in Scotland provided for in the Nurses (Scotland) Act, 1949, has been taken with the setting up of regional nurse-training committees for each of the five regional hospital board areas. The new committees will supervise the training and the promotion of research and investigation into training methods.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on November 3 the degree of B.M. was conferred, in absence, on J. D. Acland.

In Congregation on November 6 a form of statute providing for a health service for undergraduates (see *Journal*, June 23, p. 1459) was moved and adjourned *sine die* after a division. The votes recorded on the motion for the adjournment were 141 for and 41 against.

UNIVERSITY OF CAMBRIDGE

Dr. G. H. Wright and Dr. A. d'A. Bellairs have been appointed University Lecturers in Anatomy; Dr. P. A. G. Monro University Demonstrator in Anatomy; and Dr. T. S. L. Beswick University Demonstrator in Pathology, all with tenure from October 1, 1951, for three years.

UNIVERSITY OF GLASGOW

On November 3 the following degrees were conferred:

M.D.—W. M. Dennison (with high commendation).
CH.M.—J. Aitken (with commendation).
PH.D.—J. Paul.

UNIVERSITY OF EDINBURGH

On November 9 Sir Alexander Fleming, F.R.S., was elected Rector of the University, in succession to Mr. Alastair Sim. Sir Alexander Fleming is the principal of the Wright-Fleming Institute for Microbiology at St. Mary's Hospital, London, and is Professor Emeritus of Bacteriology in the University of London. He was elected F.R.S. in 1943, and two years later he was awarded the Nobel Prize for Medicine, jointly with Sir Howard Florey and Dr. E. B. Chain, for the discovery of penicillin and its healing effects.

UNIVERSITY OF LEEDS

On November 9 the Princess Royal was installed as Chancellor of the University, thus becoming the first woman Chancellor of a British university. After the ceremony her Royal Highness conferred a number of honorary degrees, including that of LL.D. on Dame Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists. Later her Royal Highness formally declared open the Parkinson building, the erection of which was made possible by the £200,000 gift of the late Dr. Frank Parkinson, a graduate of the university.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

The Harveian Oration for 1951 was delivered at the Royal College of Physicians on October 18 by Sir Archibald Gray. His subject was "The Development of Dermatology from the Time of Harvey." After a brief reference to dermatology in ancient times, a more detailed description was given of the position in the Harveian period, chiefly taken from the writings of Daniel Turner (1660–1740). Progress during the seventeenth century was noted, and the opening of a new era, heralded by the work of Willan (1757–1812) and his pupil Bateman (1778–1821), who introduced the first scientific nomenclature of skin diseases and attempted a classification based on morphology, was described. The orator then reviewed progress in the nineteenth century, when fungus infections of the skin were recognized, bacteria discovered, and substantial advances in pathology made. During that century the aetiology of skin diseases had specially occupied the attention of dermatologists, but in the twentieth century more attention was being paid to the biological reactions of the skin. The work of Lewis and of Dale had thrown light on the vascular mechanism and chemical changes which take place when the skin is damaged, and much investigation was now proceeding into immunological processes.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on November 8, with Sir Cecil Wakeley, President, in the chair, a Moynihan Lectureship was awarded to Dr. Dallas P. Phemister, Hon. F.R.C.S., of Chicago. It was reported that Dr. Cuthbert Dukes had been elected a Trustee of the Hunterian Collection. The Council received a gift of $1,000 towards the restoration fund from Mrs. James Ward Thorne.

Diplomas of Membership were awarded to the 149 successful candidates whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of November 3 (p. 1096).

The following hospitals were recognized under paragraph 23 of the Fellowship regulations: North Lonsdale Hospital, Barrow-in-Furness: additional recognition, second house-surgeon (surgical department) for six months. Victoria Hospital, Blackpool: additional recognition, general surgery, registrar (orthopaedic department), house-officer (orthopaedic and casualty department), assistant resident surgical officer, all for six months; ear, nose, and throat, senior house-officer (junior registrar); ophthalmology, senior house-officer (junior registrar). West Suffolk General Hospital, Bury St. Edmunds: surgical registrar for one year and house-surgeon (general surgery), house-surgeon (casualty and orthopaedic), both for six months. Western District Hospital, Glasgow: surgical registrar for six months. General Hospital, Hereford: senior house-officer (decennial revision). Fulham Hospital: two house-surgeons. West Norfolk Hospital, Norwich: general house-surgeon. Poole General Hospital: resident surgical officer for one year, two house-surgeons for six months. Royal Berkshire Hospital, Reading: additional recognition, registrar (ophthalmic department), registrar (ear, nose, and throat department). General Hospital, South Shields: surgical registrar for one year and house-surgeon for six months. Royal South Hants Hospital, Southampton: two house-surgeons for six months, two orthopaedic house-surgeons for six months, casualty officer for six months, registrar for one year (decennial revision). Southampton General Hospital: two house-surgeons for six months, registrar for one year. Leigh Infirmary, Wigan: resident surgical officer and casualty officer, each for six months. Royal Hampshire County Hospital, Winchester: two surgical registrars for one year, orthopaedic registrar, orthopaedic senior house-surgeon and senior house-surgeon and casualty officer, all for six months (decennial revision). Woolwich War Memorial Hospital: additional recognition of second house-surgeon for six months.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At the annual meeting of the Faculty, held on November 5, the following officers were elected for the ensuing year: *President*, Mr. W. W. Galbraith *Visitor*, Mr. Andrew Allison. *Honorary Treasurer*, Mr. Matthew White. *Honorary Librarian*, Dr. A. L. Goodall. *Representative on General Medical Council*, Mr. Andrew Allison.

The following were admitted Fellows of Faculty *qua* physician, E. J. D. Nariman, J. Sommerville; *qua* surgeon, K. K. Ghosal.

Dr. F. M. R. Walshe, F.R.S., delivered the Finlayson Memorial Lecture in the Hall of the Faculty (242, St. Vincent Street, Glasgow) on Wednesday, November 14. His subject was "Syndromes of the Thoracic Inlet and Cervico-axillary Canal."

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

The following were admitted to the Membership of the College on November 2: N. J. Ainley, M. Barry, M. Bhattacharyya, A. K. Chatterjee, S. M. A Khadri, P. N. Khan, P. Logan, E. A. Marten, S. N. Mathur, N. K. Mitra, P. M. O'Connor, R. Prasad, C. Sinnadurai, H. H. Robinson.

SOCIETY OF APOTHECARIES OF LONDON

At a meeting of the Court of Assistants of the Society, held on October 30, with Dr. G. Roche Lynch in the chair, following the Master's Day Service at the Church of St. James, Garlickhythe, Baron C. Ver Heyden de Lancey was elected to a seat on the Court by Seniority. The Master bestowed a Past Master's medal upon Mr. Duncan Fitzwilliams. Dr. J. P. Hedley was re-elected as representative of the Society on the General Medical Council for a further year. It was reported that a bequest of £700 for the general funds of the Society had been received from the estate of the late Dr. R. H. Hayes, and a bequest of £1,000 to the Sustentation Fund from the estate of the late Dr. Charles R. Box.

The following candidates were granted the Diploma of L.M.S.S.A. upon examination: W. R. Chisholm Batten, B. Vergano, M. S. Compton, E. W. Roberts.

The Gillson Scholarship in Pathology, the value of which on this occasion is £500, will be awarded in 1952. It is open to persons under the age of 35 who are Licentiates or Freemen of the Society, or who become so within six months of the award. Regulations may be obtained from the Registrar, Apothecaries' Hall, Black Friars Lane, Queen Victoria Street, London, E.C.4.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending October 27 (No. 43).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending October 27					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	35	5	13	—	3	40	3	17	1	2	886	314	40
Deaths	2	—	—	—	—	1	—	—	—	—			
Dysentery	151	47	69	—		241	19	144	—		362	247	59
Deaths		—		—			—		—				
Encephalitis, acute	5	—	1	—	1	9	1	—	—		9	1	—
Deaths		—			—		—			—			
Erysipelas			19	1	2			22	2	9			
Food-poisoning	91	15		—		160	40		1				
Infective enteritis or diarrhoea under 2 years				16	35				16	40			
Deaths	5		3	2	3	7		1	1	4			
Measles*	1,962	53	68	110	149	6,632	471	116	98	95	6,812	2,884	422
Deaths		—	—	—	—		—	—	—	—			
Meningococcal infection	35	5	18	2	2	32	2	15	—	1	57	32	22
Deaths		—	1				—	—					
Ophthalmia neonatorum	30	2	8	1		27	1	8	1		83	53	27
Pneumonia, influenzal	419	35	6	2		435	24	1	8		584	482	303
Deaths (from influenza)†	12	3	1	—	—	17	6	—	—	—			
Pneumonia, primary			119					115					
Deaths	173	33		3	2	141	24		9	8			
Poliomyelitis, acute:													
Paralytic	62	1	19	6	3	253	14	25	5	3	367	33	15
Non-paralytic	34	4											
Deaths§	6	—			—	12	—			—			
Puerperal fever			9					12					
Puerperal pyrexia‖	207	25	4	1		78	12	7	1		196	125	72
Scarlet fever	1,116	97	234	22	38	1,141	98	200	48	87	3,657	1,754	1,141
Deaths		—	—	—	—		—	—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			137	38				153	21				
(2) Tuberculosis, non-respiratory			22	10				26	5				
(1) Deaths	155	24	23	4	7	138	17	24	6	11			
(2) Deaths		3	4	—	3		2	1	—	2			
Typhoid fever	4	1	—	1	—	6	1	1	2	2			
Deaths¶	—	—	—	—		—	—	—	—		98	17	7
Paratyphoid fever	29	1	—	—	1 (B)	14	1	—	—				
Whooping-cough	1,441	48	352	45	97	3,077	295	307	29	82	3,077	1,061	749
Deaths	3	—	—	—	—	1	—	—	—	—			
Deaths (0–1 year)	208	41	27	10	13	212	37	25	7	15	391	306	212
Deaths (excluding stillbirths)	4,708	780	566	121	154	4,360	707	555	92	191	4,491	4,287	3,838
Annual death rate (per 1,000 persons living)			11·6					11·1					
Live births	6,130	1,010	764	177	337	6,561	1,080	814	236	352	8,883	6,699	5,508
Annual rate per 1,000 persons living			15·7					16·4					
Stillbirths	177	22	20			169	24	32			265	197	150
Rate per 1,000 total births (including stillborn)			26					38					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales London. and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales. and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Infectious Diseases

The only increase in the incidence of infectious diseases in England and Wales during the week ending October 27 was a rise of 153 in the number of notifications of measles. Falls were recorded for whooping-cough 75, paratyphoid fever 52, acute poliomyelitis 23, and scarlet fever 19.

The only variations of any size in the returns of measles were increases in Durham 57, Warwickshire 53, and Lancashire 41. The largest fall in the number of whooping-cough returns was 37 in London. The chief feature of the returns of scarlet fever was an increase of 38 in the number of notifications in Lancashire. The notifications of diphtheria were 2 more than in the preceding week; the largest variations in the local trends were a decrease of 6 in Lancashire and a rise of 3 in Staffordshire.

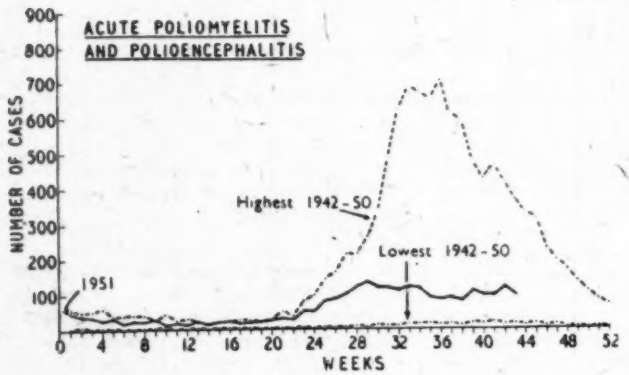
The largest return of paratyphoid fever was that of Yorkshire West Riding, where 8 cases scattered over 5 administrative areas were notified.

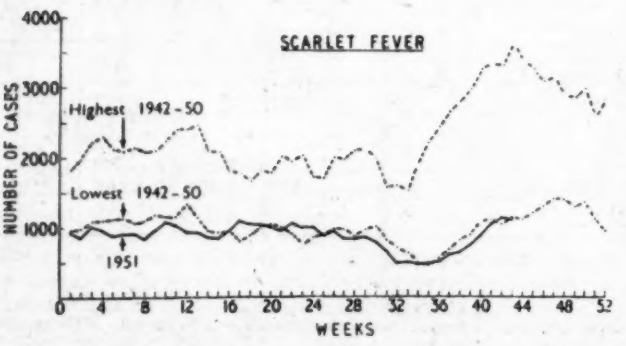
The largest returns for acute poliomyelitis during the week were Yorkshire West Riding 17 (Sheffield C.B. 3), Lancashire 6, Derbyshire 6, Kent 6 (Sittingbourne and Milton U.D. 3), London 5, Staffordshire 5.

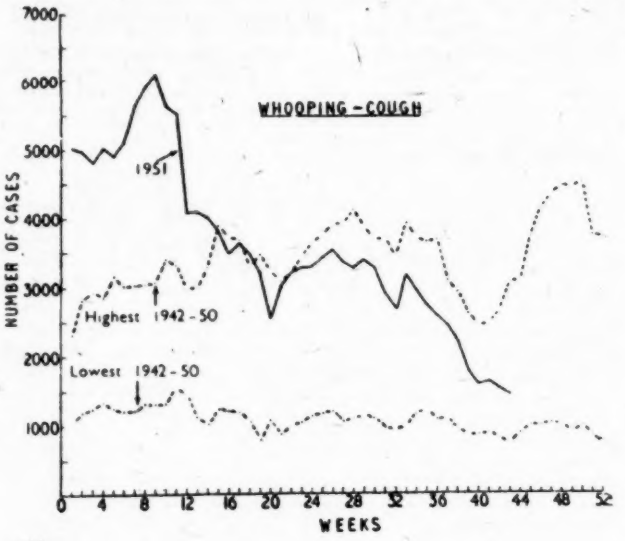
The number of notifications of dysentery was 11 fewer than in the preceding week. The largest centres of infection were London 47 (Islington 29), Middlesex 18 (Edmonton M.B. 12), Lancashire 17, Surrey 12, Gloucestershire 12.

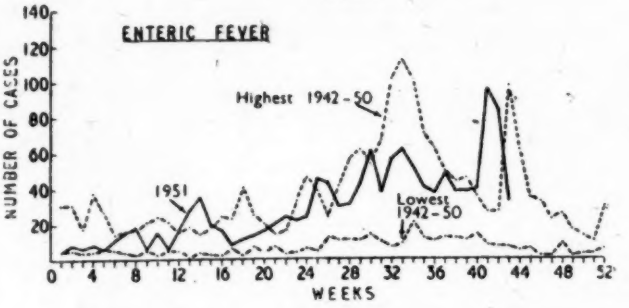
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - -, the figures for 1951 thus ———. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Quarterly Return for England and Wales

The birth rate during the June quarter of 1951 was 16.6 per 1,000. This rate was the same as in the corresponding quarter of 1950 but 2.2 below the average of the second quarters of 1945–9. The infant mortality was 28.7 per 1,000 related live births and was 0.1 above the rate for the preceding June quarter, which was the lowest rate ever recorded for a second quarter. The stillbirth rate was 22.5 per 1,000 total births and was the same as the rate for the preceding June quarter. The general death rate was 11.1 per 1,000. This rate is the same as the rate for the second quarter of 1950 and the average of the June quarters of 1945–9. Deaths attributed to acute poliomyelitis numbered 39, compared with 71, 373, 201, and 61 in the four preceding quarters.

The marriage rate was 12.0 per 1,000 and was the lowest rate for a second quarter of recent years. This was because Easter with its exceptional number of marriages fell in the first quarter of the year.

Week Ending November 3

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,067, whooping-cough 1,477, diphtheria 46, measles 1,993, acute pneumonia 510, acute poliomyelitis 82, dysentery 175, paratyphoid fever 26, and typhoid fever 2.

A competition organized by *The Builder* last year aimed to prove that a terrace house to accommodate a family of five could be built for not more than £1,000 (based on costs operating at the end of last year). Four terrace houses have just been completed near Northampton to the design placed first in the competition; the actual cost of each is £1,083, which means, state the sponsors, that four houses of this type can be built for the same cost as three built to the full Ministry standard. The extra costs were due to national increases in the price of materials and labour. The houses were erected in three and a half months, and the average number of man-hours per house was 1,690, compared with 2,575 given in the Girdwood report on the cost of building a 3-bedroom house.

Medical News

A Book for Christmas

50 Years of Medicine, containing in book form articles surveying the progress of medicine and surgery during the first half of this century which appeared in a special number of the *Journal* last year, is again available. Very pleasantly brought out, and handsomely bound, not only does it look impressive but the information it gathers together is useful and enlightening. and is of interest to both lay and medical readers. Over 300 pages of text, a complete index, and 32 illustrations make this a valuable book to have, and, incidentally, an excellent Christmas present. Costing 15s., *50 Years of Medicine* may be obtained through booksellers, or direct (post free) from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

"Any Questions?"

Early next month, in good time for Christmas, the first book of "*Any Questions?*" will be published. The book contains a selection of the best questions and answers which have appeared in the "Any Questions?" section of the *Journal* since the feature was started eight years ago. Many of these authoritative answers give practical information not yet in the textbooks. This book is confidently recommended to all practitioners. "*Any Questions?*" is strongly bound in cloth, small enough to fit the pocket, and costs 7s. 6d. (postage 6d.). Copies may be obtained on application to the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

Copies of "Thorax" Wanted

Dr. M. Urabe, Professor-designate of Surgery, Imperial University of Japan, Tokio, who has recently been visiting this country after attending the World Medical Association meetings at Stockholm, has tried without success to obtain copies of the journal *Thorax* for 1947 and 1948. Dr. Urabe intends to place the volumes in the University Medical Library. Any member who can dispose of copies of *Thorax* published during these years is asked to communicate with Dr. H. A. Sandiford, International Medical Visitors' Bureau, at B.M.A. House, Tavistock Square, W.C.1.

Chemicals in Food

A subcommittee of the Food Standards Committee (Ministry of Food) was set up in January "to review the Public Health (Preservatives, etc., in Food) Regulations and to make any recommendations the subcommittee may consider desirable for the amendment of the Regulations." Investigations will cover the use in foods of such substances as anti-oxidants, anti-mould agents, solvents, and emulsifying (including stabilizing, anti-staling, and foaming) agents, as well as preservatives and colouring matters. It is the intention that separate reports shall be prepared about each of these. Preliminary discussions show that further and more detailed information is required, particularly on biochemical, physiological, and toxicological aspects. Any person or organization able to assist is invited to write to the secretary of the subcommittee at the Ministry of Food, Food Standards and Labelling Division, 47, Portman Square, London, W.1.

Fulbright Travel Grants, 1952–3

Once again application for these financial aids to assist visits to America may be made to the United States Educational Commission in the United Kingdom, 55, Upper Brook Street, London, W.1. A full statement of the conditions of award was given in the *British Medical Journal*, 1949, 2, 1424.

Explosion at Makerere College Medical School

Early in the morning of October 25 a violent explosion took place in the new medical school buildings, and one wing was wrecked. The major destruction is in the histology preparation room, and all the apparatus and equipment is a total loss. All the student microscope and lantern-slide collections of normal and morbid anatomy, embryology, and neurology have been destroyed, as has much research material and thousands of tissue blocks. Many of the latter were burnt in the fire which followed the explosion but which was quickly extinguished. Several microscopes are damaged, and some are totally destroyed.

The glass windows of the physiology laboratories and the physiological research laboratories were extensively damaged, but only minor internal damage was sustained in these buildings. All microscope teaching has stopped and cannot recommence without outside assistance. The loss of so much necessary equipment and of all the student microscope-slide collections built up over many years is a grievous blow to the medical school, as is the heavy damage to a fine new building opened only in May this year by the Secretary of State for the Colonies (*British Medical Journal*, 1951, 1, 1444). It is feared that it will be many months before the damage can be repaired, and even longer before the slide collections and apparatus can be replaced. Any offers of help with either equipment or money will be most gratefully received by the dean of the faculty of medicine, Dr. Alexander Galloway, Medical School, P.O. Box 351, Kampala, Uganda.

North of England Obstetrical Society

A meeting of the North of England Obstetrical and Gynaecological Society was held in the University of Manchester on Friday, October 26. with the president, Dr. J. W. A. Hunter, in the chair. Professor T. N. A. Jeffcoate (Liverpool) described a case of diphallus in the female, and Dr. R. M. Corbet (Preston) reported a case of granulosa cell tumour in association with carcinoma of the uterine body and tuberculosis of the tube. Mr. H. R. Arthur and Dr. A. T. Johnson (Newcastle) read a paper on continuous caudal analgesia in the management of cervical dystocia, and Mr. H. V. Corbett (Liverpool) discussed the place for cervical incisions in modern obstetrical practice.

Leverhulme Research Fellowships

Application is invited for fellowships and grants in aid of research, intended for senior workers otherwise prevented by routine duties or pressure of other work from carrying out research. They are limited to British-born subjects normally resident in the United Kingdom; in exceptional circumstances the trustees may waive the condition of residence. The trustees will also consider applications from groups of workers engaged on co-operative programmes of research, particularly if long-term. The duration of the awards will not normally be for more than two years or

less than three months, and the amount will depend on the nature of the research and the circumstances of the applicant. Forms of application may be obtained from the secretary, Leverhulme Research Fellowships, 3–5, Salisbury Square, London, E.C.4. Applications must be received on or before December 31. Awards will be announced in May, and will date from September 1, 1952.

Epsom and Sutton Inter-hospital Psychiatric Association

This association was recently founded with the double aim of furthering clinical co-operation between the several psychiatric hospitals in the Epsom and Sutton area—i.e., Banstead, Belmont, St. Ebba's, Horton, Long Grove, The Manor, and West Park Hospitals, and their group laboratory—and of providing a local forum of contact between psychiatrists, their colleagues from other branches of medicine attached to the general hospitals, and the general practitioners of the area. An inaugural meeting was held at West Park Hospital, Epsom, on November 1, with Dr. H. R. Rollin (Horton) in the chair. Cases were presented by Drs. A. L. Kiow, B. Steinberg, and J. Zelmanowits (secretary of the association), and papers read by Dr. Oliver Garai and by Dr. J. Zelmanowits. A discussion followed. The next meeting will be held at Belmont Hospital, Sutton, on Thursday, December 6.

Emergency Bed Service: Applications and Admissions

During the seven days ending November 12 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,004, of whom 87.15% were admitted.

Professor F. E. Tylecote has been elected president of the National Smoke Abatement Society in succession to Dame Vera Laughton-Mathews.

Lieutenant-Colonel W H. Hargreaves, a senior medical specialist in the Royal Army Medical Corps, has been seconded to take up the appointment of Professor of Medicine at the Royal Medical College, Bagdad, under the Government of Iraq

The Council of the Ophthalmological Society of the United Kingdom has awarded the Treacher Collins Prize for 1951 to Mr. K. C. Wybar for his essay on "Exophthalmos in Relation to Endocrine Disorder."

COMING EVENTS

South-east Metropolitan Regional Tuberculosis Society

A meeting of the society is to be held at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1, on Saturday, November 17, at 11 a.m., when Mr. Vernon C. Thompson will deliver a lecture on "Tumours of the Lung." This meeting will be followed by the annual luncheon of the society at Messrs. Schmidt's Restaurant, Charlotte Street, W.1.

Conference on Evolution and Education

A conference will be held at the Birmingham and Midland Institute, Birmingham, on December 7 and 8. At the opening session Dr. Julian Huxley will deliver an address on the evolutionary process, and the closing address will be delivered by Professor S. Zuckerman, speaking on the evolution of the brain. The fee for admission to the conference is 10s. Tickets may be obtained from the British Social Biology Council, Tavistock House South, London, W.C.1.

Ergonomics Research Society

The society is holding a conference covering the physiological, psychological, and industrial aspects of fatigue at the College of Aeronautics, Cranfield, Bletchley, Bucks, from March 25 to 28, 1952. Full details of the programme will be available early next year.

Medical Society of London Annual Oration

Sir Heneage Ogilvie will deliver the Annual Oration, on "Whither Medicine?", before the Medical Society of London, 11, Chandos Street, Cavendish Square, W., on Monday, May 12, 1952, at 8.45 p.m.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—November 19. 4.30 p.m., lecture-demonstration for postgraduates by Dr. E. Stengel.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 19, 5 p.m., *"Trends of Opinion About the Public Health, 1901–1951. 5.—The Half-century,"* Heath Clark Lecture by Professor J. M. Mackintosh.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—November 19, 4 p.m., *"Fainting and Syncope,"* by Sir John Parkinson.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 19, 5 p.m., *"The Newer Antibiotics,"* by Professor Arnold Sorsby.

Tuesday

CHADWICK TRUST.—At the Royal Sanitary Institute, 90, Buckingham Palace Road, London, S.W., November 20, 2.30 p.m., *"The Health of Cities: Some Problems Arising from Congestion and Overbuilding,"* Bossom Gift Lecture by Professor William Holford.

DURHAM UNIVERSITY.—At Royal Victoria Infirmary, Newcastle-upon-Tyne, November 20, 5.15 p.m., *"Recent Progress in the Treatment of Fractures,"* Rutherford Morison Lecture by Sir Reginald Watson-Jones.

EUGENICS SOCIETY.—At Royal Society, Burlington House, Piccadilly, London, W., November 20. 5.30 p.m., *Symposium on Voluntary Sterilization*; speakers, Drs. C. P. Blacker, Mrs. Moya Woodside, and Mr. C. Binney, M.A.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 20, 5.30 p.m., *"Atopy,"* by Dr. F. R. Bettley.

●ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, London, S.W.—November 20, 5 p.m., *"Anticoagulants in Heart Disease,"* by Dr P. H. Wood.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—November 20, 5.30 p.m., *"The Epilepsies,"* clinical demonstration by Dr. Colin Edwards.

Wednesday

●DAVIDSON CLINIC, 58, Dalkeith Road, Edinburgh.—November 21, 8 p.m., *"Psychology and Art,"* by Miss M. C. Romanes.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 21, 5.30 p.m., *"Mycology—Epidermophyton Infections."* by Dr. R. W. Riddell.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., November 21, 4.30 p.m., *"How the Laboratory Can Help in Intractable Urinary Infections,"* by Dr. R. Thomson.

●LONDON MARRIAGE GUIDANCE COUNCIL, 78, Duke Street, Grosvenor Square, W.—November 21, 6 p.m., *"The Physical Aspects of Marriage Relationships,"* by Dr. Philip M. Bloom

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road. W.—November 21, 11.45 a.m., medical clinical-pathological conference.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—November 21, 3.30 p.m., *"The Control of Infectious Disease by Local Authorities,"* by Dr. V. Freeman.

Thursday

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY, The Union, University Avenue, Glasgow.—November 22, 7.30 p.m., *"The Circulation in the Normal and the Diseased Kidney,"* by Professor J. Trueta.

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, November 22, 5 p.m., *"Megaloblastic Anaemia of Pregnancy and the Puerperium,"* by Dr. J. R. Clark.

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—November 22, 5 p.m., *"The Welfare Centre,"* by Dr. E. W. Hart.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—November 22, 3 p.m., *"The Relationship Between the Electrical Activity of the Brain and Adaptive Behaviour,"* by Mr. W. Grey Walter, Sc.D.

LIVERPOOL MEDICAL INSTITUTION.—At the Radium Institute, Myrtle Street, Liverpool, November 22, 2.30 p.m., afternoon clinical demonstration.

MEDICO-LEGAL SOCIETY.—At 26, Portland Place, London, W., November 22, 8.15 p.m., *"The Functions of the Forensic Science Laboratory in Criminal Investigations,"* by Dr. H. S. Holden.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—November 22, 5 p.m., *"Samuel Pepys,"* Lloyd Roberts Lecture by Mr. Arthur Bryant.

RESEARCH DEFENCE SOCIETY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street. W.C., November 22, 5.30 p.m., *"Research and Administration—A Profitable Partnership?"* Stephen Paget Memorial Lecture by Sir Wilson Jameson. Followed by annual general meeting of the society

●ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, London, S.W.—November 22, 5 p.m., *"The Treatment of Heart Failure,"* by Dr. William Evans.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 22, 5 p.m., *"Studies of Human Gastric Function,"* Arris and Gale Lecture by Mr. J. N. Hunt.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, November 22, 5 p.m., *"The Spleen in Medicine,"* by Sir John W. McNee.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—November 22, 4.30 p.m., lecture-demonstration in psychiatry by Dr. D. Curran.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At South Kensington Hotel, 41, Queen's Gate Terrace, London, S.W., November 22, 7.30 for 7.45 p.m., *"General Practice, the Hospitals, and the Future,"* Presidential Address by Mr. B. Sangster Simmonds.

Friday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 23, 5.30 p.m., *"Bacterial Aspects of Immunity,"* by Dr. A. A. Miles.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 23, 5.30 p.m., *"Atopic Eczema,"* clinical demonstration by Dr. F. R. Bettley.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, Royal National Throat, Nose and Ear Hospital, Gray's Inn Road, London, W.C.—November 23, 4.30 p.m., *"Plastic Surgery and the Upper Air Passages,"* by Sir Harold Gillies. Annual address.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—November 23, 11.15 a.m., surgical clinical-pathological conference; 2 p.m., *"The Surgical Treatment of Idiopathic Colitis and its Complications,"* by Mr. E. C. B. Butler; 4 p.m., *"Diagnosis and Treatment of Hyperthyroidism,"* by Professor E. J. Wayne.

●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS, 58, Queen Anne Street, London, W.—November 23, 5 p.m., *"Obstetrics and Gynaecology in Relation to Thyrotoxicosis and Myasthenia Gravis,"* William Blair-Bell Memorial Lecture by Mr. G. L. Keynes.

●ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, London, S.W.—November 23, 5 p.m., *"Medical Aspects of Prolapsed Intervertebral Disk,"* by Dr. Michael Kremer.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—November 23, 8 p.m., *"Respiratory Diseases: Fact and Fiction,"* by Professor David Whitteridge.

WELSH NATIONAL SCHOOL OF MEDICINE.—At Institute of Pathology, The Royal Infirmary, Cardiff, November 23, 5 p.m., *"The Arterial Lining,"* Kettle Memorial Lecture by Professor J. B. Duguid.

Saturday

BRITISH ASSOCIATION OF FORENSIC PATHOLOGISTS.—At Guy's Hospital Medical School, London, S.E., November 24, 9.30 a.m., *"The Interpretation of Asphyxial Signs"* and *"Separate Existence,"* discussion, open to all pathologists. Names should be sent in advance to honorary secretary, Dr. F. E. Camps, 79, Harley Street, London, W.1.

NATIONAL ASSOCIATION OF PROBATION OFFICERS (COUNTY OF ESSEX BRANCH).—At Council Chamber, Walthamstow Town Hall, London, E., November 24, 2.30 p.m., *"The Court and the Sexual Offender,"* by Sir Norwood East.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Baxter.—On October 31, 1951, at Larches, Catisfield, Fareham, Hants, Charles Thomas Baxter, M.R.C.S., L.R.C.P., Surgeon Captain, R.N., retired, aged 73.

Buttar.—On November 8, 1951, at Westwood, Wilton Road, Salisbury, Fernie Louden Buttar, M.B., Ch.B.

Clarkson.—On November 6, 1951, at Little Cambus, Doune, Perthshire, Robert Durward Clarkson, M.D., F.R.C.P.Ed., aged 84.

Comerford.—On November 4, 1951, Charles Henry Comerford, M.D., D.P.H., aged 57.

Dywien.—On November 10, 1951, Judah Dywien, M.R.C.S., L.R.C.P.

English.—On November 9, 1951, at Beech Close, Newmarket Road, Norwich, Samuel English, M.B., F.R.C.S.I., aged 80.

Leech.—On November 5, 1951, at the Devizes and District Hospital, John Frederick Wolseley Leech, M.D., D.P.M., of Dormer Cottage, Devizes, Wilts, aged 70.

McGlade.—On November 8, 1951, Francis Joseph McGlade, M.B., B.Ch., of Blackley, Manchester.

Millar.—On November 10, 1951, Jane Ogilvie Millar, M.D., D.P.H., D.Obst.R.C.O.G., of 25, Gorse Road, Blackburn, Lancs.

Orr.—On November 3, 1951, in hospital, Thomas Stewart Allan Orr, M.B., Ch.B., of Warrender Park Crescent, Edinburgh.

Rinkel.—On November 10, 1951, at High Garth, Nayland, near Colchester, Essex, Lambert Ronald Joslin Rinkel, M.R.C.S., L.R.C.P.

Wiseman.—On November 4, 1951, at his home, 18, Watling Street Road, Fulwood, Preston, Lancs, David Chalmers Wiseman, M.B., F.R.C.S.Ed., M.R.C.O.G., aged 36.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Foreign Clinics for Asthma and Bronchitis

Q.—*What can clinics abroad—e.g., in Switzerland—offer to sufferers from chronic bronchitis and asthma that is not obtainable in this country? Is treatment abroad recommended in obstinate cases?*

A.—The dust and pollen content of air diminishes with increasing height. This is probably the chief reason for the benefit which asthmatic patients derive from a stay in Switzerland. It is reasonable to suppose that non-specific irritants such as are present in damp and foggy air are also less common. It is important to remember when sending patients to Switzerland that certain low-lying areas, where mists lie in the folds of the hills, are generally agreed to be unsatisfactory for the asthmatic. It is also inadvisable to send patients with asthma and associated emphysema to places situated more than 5,000 ft. (1,524 m.) above sea-level. Certain places in France, such as Bourboule and Mont Dore, have a special reputation for the treatment of asthma. Stress is laid on the importance of the inhalation of natural vapour which contains a high proportion of carbon dioxide, and asthmatics who visit these places have the advantage of a graduated regimen prescribed by specialists who deal mainly with asthmatic patients.

It is doubtful if there is any advantage in sending patients with chronic bronchitis to Switzerland; the important requirement in their case is warm air, and for this reason the South of France, the Italian Riviera, or North Africa are more suitable. The South Coast of England also suits many patients with chronic bronchitis.

Fatal Wasp Stings

Q.—*The daily press has reported recently three fatal cases of wasp sting, death occurring with great rapidity in 15 minutes to one hour. What are the early signs and symptoms in these unusual fatal cases? How should the patients be treated?*

A.—The early signs and symptoms in fatal cases of wasp sting are similar to those of any severe anaphylactic reaction, such as may occur after the administration of serum or after an excessive dose of an allergen in a highly sensitive patient. Usually the first symptom is an intense pruritus followed by a rapidly developing severe angioneurotic oedema and severe dyspnoea of asthmatic type. Palpitation and precordial pain may be complained of, and the pulse, which at first is full and bounding, soon becomes rapid and thready as the blood pressure falls. Vomiting, severe colicky abdominal pain, or diarrhoea may occasionally usher in the attack, but more commonly the gastro-intestinal symptoms follow on the oedema and dyspnoea. Nervous symptoms—i.e., ringing in the ears—a sense of heavy pressure in the head, or sudden unconsciousness not infrequently followed by convulsions, may also be the first symptoms, and occasionally the only symptoms.

Every person who knows he is allergic to wasp or bee stings should carry ephedrine or *iso*propyl-*nor*-adrenaline and an antihistaminic, to be taken as soon as he is stung. Treatment of the attack consists in giving adequate adrenaline subcutaneously as soon as possible, 0.5 to 1 ml., and more adrenaline is indicated if the patient's condition is deteriorating. Adrenaline should also be injected into the site of the sting, and where possible a tourniquet should be applied proximally to the site to impede the venous return.

Intravenous aminophylline (0.5 g. in 20 ml.) should be given whenever there is severe asthmatic dyspnoea, for its effect is often rapidly and dramatically beneficial. That adrenaline (1 in 1,000) intravenously is dangerous should be remembered, for it needs to be diluted (1 ml. in 250 ml. of normal saline) for intravenous use. It has been suggested as an emergency measure that a small dose of adrenaline (1 in 1,000—0.2 ml.) might be diluted up to 5 ml. with the patient's own blood and then given very slowly intravenously. After the acute episode is under control, an antihistamine will help to prevent the later exacerbations which are liable to occur in the more severe cases.

Generalized Hyperidrosis

Q.—*A patient of mine, aged 57, has suffered from very severe hyperidrosis as long as he can remember, especially of the hands, axillae, and feet. I understand that chemical sympathectomy (injection with 6% phenol) has been used successfully in the treatment of hyperidrosis of the feet. Would such treatment be useful in this case? If not, what treatment is advised?*

A.—It is assumed from the wording of the question that the patient is otherwise healthy. Generalized hyperidrosis is frequently a psychosomatic disturbance—patients with this symptom presenting many features of chronic anxiety. In view of this patient's age, however, it is unlikely that psychotherapy will have anything to offer. The use of the new ganglion-blocking agents is the only approach likely to produce amelioration of the generalized excessive sweating. It would be worth while trying the effect of hexamethonium bromide, starting with doses of 100 mg. four times daily by mouth and working up the level of tolerance, keeping a close observation for the development of untoward side-effects, in particular postural hypotension.

Lumbar sympathectomy is now such a safe and simple procedure in skilled surgical hands that the use of phenol injection of the sympathetic system is now usually reserved for cases in which the patient's general condition or some other factor excludes operative approach. Such surgical sympathectomy would relieve the hyperidrosis of the feet almost certainly, but would, of course, leave the condition of the hands and axillae much as before.

Finally, close attention should be given to the nature of the footwear. Open-weave porous socks should be used, and often the wearing of sandals helps considerably. Crêpe or rubber soles should be avoided.

Teeth of Africans

Q.—*The African population of Southern Rhodesia among whom I work is reputed in the past to have had good teeth, and this is supported by the excellent though somewhat worn teeth of the older people. The children of to-day, however, have poor teeth, the milk teeth often wearing and going carious soon after they are cut, and the permanent teeth are little better. Young adults often show a good-looking set of teeth prematurely worn down. The first child in any family almost always has worse teeth than the later ones, the second is not quite so bad, and later ones show only a saw-edge to the incisors. Is there any simple, cheap, and effective treatment? At present I give all pregnant women calcium gluconate in solution, and make up children's medicines with the same solution when compatibility allows, and I am trying to popularize a calcium gluconate and vitamin-D tablet as a sweet among the children. Is this any use, or is it too late to do anything after the antenatal period or after the permanent teeth have started to come through?*

A.—Milk and cod-liver or halibut-liver oil (as such or in capsule form) provide the simplest means of defeating defective dental calcification and undoubtedly play an important part in preventing the onset and spread of caries. These supplements are effective both ante- and post-natally, but they are best given to the mother during pregnancy and lactation and to the offspring from infancy up to adolescence at least. Most soluble calcium salts can replace milk if this is scarce. The mineral intake can be further reinforced by cheese, cabbage, animal protein, etc., while reduced consumption of cereal and other largely carbohydrate foods is also beneficial.

Dental Caries and Anaemia

Q.—*Is anaemia an aetiological factor in dental caries?*

A.—This suggestion cannot be supported on the available evidence. With gingivitis the state of the blood is of great importance, since the defence mechanism of the gums depends on the efficiency of the blood supply. In blood diseases such as the leukaemias, agranulocytosis, etc., an instant reflection is seen in the gums, where a fairly acute gingivitis is almost invariably seen. Similarly, deposition of heavy metals, such as bismuth and lead, in the gingival tissues almost always leads to a gingivitis, due to interference with the blood supply. With dental caries, however, it is an entirely different matter, since the attack on the tooth is clearly independent of the blood supply. The enamel is a non-vital tissue, and the attack cannot be halted by a greater or more efficient blood supply. Equally, the dentine, although bathed in tissue fluid, does not have a true blood supply. The evidence at present is that the state of the blood has no influence on the progress of dental caries.

Angioneurotic Oedema and Hormones

Q.—*What place has hormone therapy in the treatment of angioneurotic oedema? Is cortisone or adrenocorticotrophic hormone effective? I have heard that thyroid extract may sometimes be successful.*

A.—Angioneurotic oedema, or giant urticaria, is usually regarded as an allergic manifestation differing from ordinary urticaria in that it occurs in the subcutaneous or submucous tissues rather than in the skin. The precipitating cause may be indeterminate or emotional, cold or food sensitization. It has been treated successfully with adrenaline, ephedrine, and antihistaminic drugs. More recently cortisone and adrenocorticotrophic hormone have both been found to be effective. This was referred to recently in an annotation in this *Journal* (September 1, 1951, p. 534), in which a special report of the *Bulletin of the Johns Hopkins Hospital* (87, No. 5, 1950) was reviewed. The writer has not heard of thyroid extract being efficacious, but oestrogens are sometimes given in the climacteric with some favourable response.

Gas Heaters and Metallic Poisoning

Q.—*Is there any risk of metallic poisoning from using a domestic gas water-heater for making tea or other culinary purposes?*

A.—The parts of an instantaneous-type gas water-heater in contact with the water are copper or brass, and may be bare, tinned, or lacquered. Any toxic hazard would therefore only arise from the presence of copper in the water. One manufacturer had an analysis carried out on the hot water, and it contained less than 0.1 part per million of copper. The permitted limit in drinking-water in the United States is 0.2 p.p.m.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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